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(71) Applicant *(for all designated States except US)*: **GEORGETOWN UNIVERSITY** [US/US]; 37th & O Streets Northwest, Washington, DC 20057-1408 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KOZIKOWSKI, Alan, P.** [US/US]; 2222 North Dayton Street, Chicago, IL 60614 (US). **GLAZER, Robert, I.** [US/US]; 11352 Palatine Drive, Potomac, MD 20854 (US). **PETUKHOV, Pavel** [RU/US]; 12209 Village Square Terrace, Apt. 401, Rockville, MD 20852 (US). **WEI, Zhi-Liang** [CN/US]; 4582 Mac Arthur Blvd, NW, Apt. 204, Washington, DC 20007 (US).

(74) Agents: **GORDON, Dana, M.** et al.; Patent Group, Foley Hoag Llp, 155 Seaport Boulevard, Boston, MA 02210 (US).

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(54) Title: LIGANDS FOR THE PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR, AND METHODS OF USE THEREOF

(57) Abstract: One aspect of the present invention relates to compounds that are active at a peroxisome proliferator-activated receptor (PPAR). In certain embodiments, the compound has a isoxazole or indole core. Another aspect of the present invention relates to a method of treating a mammal afflicted with cancer or non-insulin-dependent (type II) diabetes by administering a therapeutic amount of the compounds of the invention. In certain embodiments, the invention relates to a method of treating prostrate, stomach, or breast cancer. Another aspect of the invention relates to a method of identifying ligands active at a PPAR subtype using X-ray structural information. In certain embodiments, the method of identifying the ligand comprises using molecular modeling approaches including: *in silico* screening of chemical databases, *de novo*/rational drug design in which the ligand will be created computationally, and/or *in silico* screening of virtual combinatorial libraries.

Ligands for the Peroxisome Proliferator-Activated Receptor, and Methods of Use Thereof

Background of the Invention

Peroxisome Proliferator-Activated Receptors

The peroxisome proliferator-activated receptor (PPAR) is a member of the nuclear receptor superfamily, and consists of three isoforms, PPAR α, β/δ and γ; there are two splice variants of PPARγ, denoted as PPARγ1 and PPARγ2. Neve, B. P.; Fruchart, J.; Staels, B., *Biochem Pharmacol* **2000**, *60*, 1245-1250; Clarke, S. D.; Thuillier, P.; Baillie, R. A.; Sha, X., *Am J Clin Nutr* **1999**, *70*, 566-571; Sundvold, H.; Brzozowska, A.; Lien, S., *Biochem Biophys Res Commun* **1997**, *239*, 857-861. PPARs are lipid-regulated transcription factors that are activated by agents known to produce peroxisome proliferation, and regulate the expression of genes involved primarily in the oxidation and synthesis of lipids. PPARγ is expressed predominantly in adipose tissue and the intestine, but also in the mammary gland, endothelial cells, smooth muscle and macrophages; in human adipose tissue, PPARγ1 is more highly expressed than PPARγ2. Braissant, O.; Foufelle, F.; Scotto, C.; Dauca, M.; Wahli, W., *Endocrinology* **1996**, *137*, 354-366; Braissant, O.; Wahli, W., *Endocrinology* **1998**, *139*, 2748-2754; Mansen, A.; Guardiola-Diaz, H.; Rafter, J.; Branting, C.; Gustafsson, J. A., *Biochem Biophys Res Commun* **1996**, *222*, 844-851; Tontonoz, P.; Nagy, L.; Alvarez, J. G.; Thomazy, V. A.; Evans, R. M., *Cell* **1998**, *93*, 241-252; Fajas, L.; Auboeuf, D.; Raspe, E.; Schoonjans, K.; Lefebvre, A. M. et al., *J Biol Chem* **1997**, *272*, 18779-18789.

PPARγ is the major isoform expressed in the mammary gland as well as in primary and metastatic breast cancer and breast cancer cell lines, and PPARγ2 is the predominant variant in these tissues. Elstner, E.; Muller, C.; Koshizuka, K.; Williamson, E. A.; Park, D. et al., *Proc Natl Acad Sci U S A* **1998**, *95*, 8806-8811; Mehta, R. G.; Williamson, E.; Patel, M. K.; Koeffler, H. P., *J Natl Cancer Inst* **2000**, *92*, 418-423; Mueller, E.; Sarraf, P.; Tontonoz, P.; Evans, R. M.; Martin, K. J. et al., *Mol Cell* **1998**, *1*, 465-470; Gimble, J. M.; Pighetti, G. M.; Lerner, M. R.; Wu, X.; Lightfoot, S. A. et al., *Biochem Biophys Res Commun* **1998**, *253*, 813-817. Expression of PPARγ disappears in the lactating mouse mammary gland as well as in DMBA-induced rat mammary tumors. Gimble, J. M.; Pighetti, G. M.; Lerner, M. R.; Wu, X.; Lightfoot, S. A. et al., *Biochem Biophys Res*

Commun **1998**, *253*, 813-817. PPARγ agonists have antidiabetic activity in type II diabetes by enhancing glucose and fatty acid metabolism in peripheral tissues such as muscle. Beger, J.; Moller, D.E. *Annu Rev Med* **2002**, *53*, 409-435.

PPARs contains the structural features characteristic of nuclear hormone receptors, including a DNA-binding domain (DBD) containing two zinc fingers, a ligand-binding domain (LBD) containing a large hydrophobic pocket as well as a ligand-dependent transactivation region (AF-2) at the C-terminus and a lesser characterized, putative N-terminal transactivation domain (AF-1). PPAR isoforms share a common domain structure and molecular mechanism of action. Human PPARδ, PPARα, and PPARγ contain a conserved domain structure with a DNA binding domain (*DBD*) and ligand-binding domain (*LBD*). PPARγ$_1$ and PPARγ$_2$ are distinguished by 30 extra amino acids at the N terminus of PPARγ$_2$ (from Rosen & Spiegelman, *J. Biol. Chem.* 276:37731, 2001). The PPAR functions as a heterodimeric transcription factor with members of the retinoid X receptor (RXR) transcription factor family, and requires high-affinity binding of PPAR- and RXR-specific ligands to their respective receptors to engage transcription. Mukherjee, R.; Jow, L.; Croston, G. E.; Paterniti, J. R., Jr., *J Biol Chem* **1997**, *272*, 8071-8076. The PPAR/RXR heterodimer binds to the PPAR response element (AGGTCANAGGTCA). The interaction of PPAR:RXR with the transcriptional machinery occurs through interaction with either coactivators, such as C/EBP, SRC-1 (steroid receptor coactivator protein 1) and DRIP205 or the corepressors SMRT, and even PPARα itself, which acts in a dominant-negative fashion with RXRα. Nanbu-Wakao, R.; Fujitani, Y.; Masuho, Y.; Muramatu, M.; Wakao, H., *Mol Endocrinol* **2000**, *14*, 307-316; Yang, W.; Rachez, C.; Freedman, L. P., *Mol Cell Biol* **2000**, *20*, 8008-8017; DiRenzo, J.; Soderstrom, M.; Kurokawa, R.; Ogliastro, M. H.; Ricote, M. et al., *Mol Cell Biol* **1997**, *17*, 2166-2176; Nagy, L.; Kao, H. Y.; Love, J. D.; Li, C.; Banayo, E. et al., *Genes Dev* **1999**, *13*, 3209-3216; Jow, L.; Mukherjee, R., *J Biol Chem* **1995**, *270*, 3836-3840. These interactions provide the switch for controlling complex programs of gene expression in target tissues. Yang, W.; Rachez, C.; Freedman, L. P., *Mol Cell Biol* **2000**, *20*, 8008-8017.

Several mutations and polymorphisms in PPARγ have been identified, such as Lys319X and Gln286Pro in sporadic colon cancer that were associated with loss of DNA binding and ligand-dependent transcription by the PPARγ agonists troglitazone (TGZ) and 15-deoxy-$\Delta^{12,14}$-prostaglandin J2 (PGJ2). Sarraf, P.; Mueller, E.; Smith, W. M.; Wright, H.

M.; Kum, J. B. et al., *Mol Cell* **1999**, *3*, 799-804. Similar results were found for PPARγ2 polymorphism Pro112Ala; in contrast, polymorphism Ser114Ala resulted in increased transactivation activity by presumably blocking the inhibitory effect of Ser114 phosphorylation by MAP kinases. Deeb, S. S.; Fajas, L.; Nemoto, M.; Pihlajamaki, J.; Mykkanen, L. et al., *Nat Genet* **1998**, *20*, 284-287; Ristow, M.; Muller-Wieland, D.; Pfeiffer, A.; Krone, W.; Kahn, C. R., *N Engl J Med* **1998**, *339*, 953-959; Shao, D.; Lazar, M. A., *J Biol Chem* **1997**, *272*, 21473-21478. Recently, the t(2;3)(q13;p25) translocation associated with thyroid follicular carcinoma was found to encode the PAX8-PPARγ1 fusion protein. Kroll, T. G.; Sarraf, P.; Pecciarini, L.; Chen, C. J.; Mueller, E. et al., *Science* **2000**, *289*, 1357-1360. This chimeric PPAR acted in a dominant-negative manner to suppress PPARγ1 ligand-mediated transactivation, supporting the hypothesis that the wild-type PPARγ acts as a tumor suppressor.

PPARγ Ligands as Antitumor and Chemopreventive Therapy

PPARγ ligands have been shown to have chemopreventive and antitumor effects in a number of animal model systems. Kopelovich, L.; Ray, J. R.; Glazer, R. I.; Crowell, J. A., *Mol Cancer Ther* **2002**, *1*, 357-363; Rosen, E. D.; Spiegelman, B. M., *J Biol Chem* **2001**, *276*, 37731-37734. Either TGZ or the RAR ligand, all-*trans* retinoic acid, prevented DMBA-induced preneoplastic lesions in mammary gland organ cultures. Significantly, the selective RXR ligand, LG10068, although ineffective alone, acted synergistically with TGZ to inhibit these lesions. Mehta, R. G.; Williamson, E.; Patel, M. K.; Koeffler, H. P., *J Natl Cancer Inst* **2000**, *92*, 418-423. This result suggests that the therapeutic use of a cocktail of ligands for each heteromeric partner may be more effective than use of the individual ligands. TGZ and the PPARα agonist, WY14643, were effective chemopreventive agents against DMBA-mediated rat mammary tumorigenesis, and the PPARγ agonist, GW7845, which is 1000-fold more potent than TGZ, markedly reduced nitroso-methyl-urea-mediated mammary tumorigenesis. Pighetti, G. M.; Novosad, W.; Nicholson, C.; Hitt, D. C.; Hansens, C. et al., *Anticancer Res* **2001**, *21*, 825-829; DeLuca, J. G.; Doebber, T. W.; Kelly, L. J.; Kemp, R. K.; Molon-Noblot, S. et al., *Mol Pharmacol* **2000**, *58*, 470-476; Cobb, J. E.; Blanchard, S. G.; Boswell, E. G.; Brown, K. K.; Charifson, P. S. et al., *J Med Chem* **1998**, *41*, 5055-5069; Suh, N.; Wang, Y.; Williams, C. R.; Risingsong, R.; Gilmer, T. et al.; *Cancer Res* **1999**, *59*, 5671-5673.

The effectiveness has been demonstrated of PPARγ agonists as anticancer agents in

breast, prostate, stomach, lung, colon and pancreatic tumor cell lines. Elstner, E.; Muller, C.; Koshizuka, K.; Williamson, E. A.; Park, D. et al. Ligands for peroxisome proliferator-activated receptorgamma and retinoic acid receptor inhibit growth and induce apoptosis of human breast cancer cells *in vitro* and in BNX mice. *Proc Natl Acad Sci U S A* **1998**, *95*, 8806-8811; Mueller, E.; Sarraf, P.; Tontonoz, P.; Evans, R. M.; Martin, K. J. et al. Terminal differentiation of human breast cancer through PPAR gamma. *Mol Cell* **1998**, *1*, 465-470; Clay, C. E.; Namen, A. M.; Atsumi, G.; Willingham, M. C.; High, K. P. et al. Influence of J series prostaglandins on apoptosis and tumorigenesis of breast cancer cells. *Carcinogenesis* **1999**, *20*, 1905-1911; Tsubouchi, Y.; Sano, H.; Kawahito, Y.; Mukai, S.; Yamada, R. et al., *Biochem Biophys Res Commun* **2000**, *270*, 400-405; Tontonoz, P.; Singer, S.; Forman, B. M.; Sarraf, P.; Fletcher, J. A. et al.; *Proc Natl Acad Sci U S A* **1997**, *94*, 237-241; Kubota, T.; Koshizuka, K.; Williamson, E. A.; Asou, H.; Said, J. W. et al., *Cancer Res* **1998**, *58*, 3344-3352; Itami, A.; Watanabe, G.; Shimada, Y.; Hashimoto, Y.; Kawamura, J. et al., *Int J Cancer* **2001**, *94*, 370-376; Koga, H.; Sakisaka, S.; Harada, M.; Takagi, T.; Hanada, S. et al., *Hepatology* **2001**, *33*, 1087-1097; Hisatake, J. I.; Ikezoe, T.; Carey, M.; Holden, S.; Tomoyasu, S. et al., *Cancer Res* **2000**, *60*, 5494-5498; Takahashi, N.; Okumura, T.; Motomura, W.; Fujimoto, Y.; Kawabata, I. et al., *FEBS Lett* **1999**, *455*, 135-139; Motomura, W.; Okumura, T.; Takahashi, N.; Obara, T.; Kohgo, Y., *Cancer Res* **2000**, *60*, 5558-5564; Mueller, E.; Smith, M.; Sarraf, P.; Kroll, T.; Aiyer, A. et al., *Proc Natl Acad Sci U S A* **2000**, *97*, 10990-10995.

TGZ and all-*trans*-retinoic acid acted synergistically to inhibit the proliferation of MCF-7 breast cancer cells *in vitro*, as well as MCF-7 xenografts in nude mice, by reducing the levels of Bcl-2 and inducing apoptosis. Elstner, E.; Muller, C.; Koshizuka, K.; Williamson, E. A.; Park, D. et al., *Proc Natl Acad Sci U S A* **1998**, *95*, 8806-8811. In PANC-1 pancreatic carcinoma cells, TGZ and 9-*cis*-retinoic acid were additive in causing G1 cell cycle arrest resulting from reduced expression of cyclin D1 and HB-EGF due to inhibition of the transcriptional activities of AP-1 and Ets. Kitamura, S.; Miyazaki, Y.; Hiraoka, S.; Nagasawa, Y.; Toyota, M. et al., *Int J Cancer* **2001**, *94*, 335-342. The antitumor activity of TGZ may also be due, at least in part, to inhibition of aromatase activity and estrogen biosynthesis in mammary gland adipose stromal tissue, which would increase TGZ's effectiveness against estrogen receptor-positive breast cancer. Rubin, G. L.; Zhao, Y.; Kalus, A. M.; Simpson, E. R., *Cancer Res* **2000**, *60*, 1604-1608. Therefore,

PPARγ activation by selective ligands will likely lead to reduced tumor incidence, tumor growth and progression.

Moreover, PPARγ agonists are effective anti-inflammatory drugs by directly associating with and inhibiting NFκB; thus, these drugs may be efficacious in treating precancerous conditions, such as colitis. Ricote, M.; Li, A. C.; Willson, T. M.; Kelly, C. J.; Glass, C. K., *Nature* **1998**, *391*, 79-82; Jiang, C.; Ting, A. T.; Seed, B., *Nature* **1998**, *391*, 82-86; Patel, L.; Pass, I.; Coxon, P.; Downes, C. P.; Smith, S. A. et al.,*Curr Biol* **2001**, *11*, 764-768; Chung, S. W.; Kang, B. Y.; Kim, S. H.; Pak, Y. K.; Cho, D. et al., *J Biol Chem* **2000**, *275*, 32681-32687; Tamura, M.; Gu, J.; Takino, T.; Yamada, K. M., *Cancer Res* **1999**, *59*, 442-449; Su, C. G.; Wen, X.; Bailey, S. T.; Jiang, W.; Rangwala, S. M. et al., *J Clin Invest* **1999**, *104*, 383-389.

A molecular basis for the antiproliferative and chemopreventive activity of PPARγ is suggested by several studies. PPARγ was found to activate transcription of the PTEN tumor suppressor gene in MCF-7 breast cancer cells and Caco-2 colon cancer cells by binding to two PPAR response elements in the PTEN promoter. Patel, L.; Pass, I.; Coxon, P.; Downes, C. P.; Smith, S. A. et al., *Curr Biol* **2001**, *11*, 764-768. *Because PTEN is a 3-phosphoinositide phosphatase, which negatively regulates cell survival, it would be expected that PPARγ activation would induce or sensitize cells to apoptosis.* Di Cristofano, A.; Pandolfi, P. P., *Cell* **2000**, *100*, 387-390. PPARγ agonists also inhibit transit through the G1/S cell cycle. TGZ increased the levels of the cyclin-dependent protein kinase inhibitor, $p27^{Kip1}$, in pancreatic and liver carcinoma cells. Itami, A.; Watanabe, G.; Shimada, Y.; Hashimoto, Y.; Kawamura, J. et al., *Int J Cancer* **2001**, *94*, 370-376; Koga, H.; Sakisaka, S.; Harada, M.; Takagi, T.; Hanada, S. et al., *Hepatology* **2001**, *33*, 1087-1097; Motomura, W.; Okumura, T.; Takahashi, N.; Obara, T.; Kohgo, Y., *Cancer Res* **2000**, *60*, 5558-5564. Cyclin D1 expression is upregulated by NFκB, and therefore, inhibition of NFκB by PPARγ agonists may be an additional point of intervention for inhibiting the cell cycle. Henry, D. O.; Moskalenko, S. A.; Kaur, K. J.; Fu, M.; Pestell, R. G. et al., *Mol Cell Biol* **2000**, *20*, 8084-8092; Chung, S. W.; Kang, B. Y.; Kim, S. H.; Pak, Y. K.; Cho, D. et al., *J Biol Chem* **2000**, *275*, 32681-32687. Because reduction in p27 and dysregulation of cyclins D1 and E is a common feature of many human cancers, the ability of PPARγ agonists to downregulate the G1/S cell cycle and negatively regulate survival, establishes a rational basis for their use as anticancer and chemopreventive drugs. Loda, M.; Cukor, B.;

Tam, S. W.; Lavin, P.; Fiorentino, M. et al., *Nat Med* **1997**, *3*, 231-234; Tan, P.; Cady, B.; Wanner, M.; Worland, P.; Cukor, B. et al., *Cancer Res* **1997**, *57*, 1259-1263; Esposito, V.; Baldi, A.; De Luca, A.; Groger, A. M.; Loda, M. et al., *Cancer Res* **1997**, *57*, 3381-3385; Sherr, C. J., *Science* **1996**, *274*, 1672-1677.

PPAR Ligands

Figure 2 depicts a number of compounds that show some activity at one or more of the PPARs. Willson, T. M.; Brown, P. J.; Sternbach, D. D.; Henke, B. R., *J Med Chem* **2000**, *43*, 527-550. The antidiabetic agents known as the thiazolidinediones or glitazones were the first high affinity PPARγ agonists to have been described, although they were not originally developed as PPARγ ligands. Lehmann, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkison, W. O.; Willson, T. M. et al., *J Biol Chem* **1995**, *270*, 12953-12956; Kliewer, S. A.; Umesono, K.; Noonan, D. J.; Heyman, R. A.; Evans, R. M., *Nature* **1992**, *358*, 771-774; Kliewer, S. A.; Lenhard, J. M.; Willson, T. M.; Patel, I.; Morris, D. C. et al., *Cell* **1995**, *83*, 813-819. α-Alkoxy-β-phenylpropanoic acids such as SB 213068 have been reported to possess dual PPARα/γ activity. Buckle, D. R.; Cantello, B. C. C.; Cawthorne, M. A.; Coyle, P. J.; Dean, D. K. et al., *Bioorganic & Medicinal Chemistry Letters* **1996**, *6*, 2121-2126. A series of tyrosine-based PPARγ agonists, such as GW1929, were the first antidiabetic drugs to be optimized based on their activity for human PPARγ. Henke, B. R.; Blanchard, S. G.; Brackeen, M. F.; Brown, K. K.; Cobb, J. E. et al., *J Med Chem* **1998**, *41*, 5020-5036. GW0072 is a PPARγ agonist that was identified in PPAR transactivation and adipocyte differentiation assays; however, it acts as a partial agonist because it does not contact the AF-2 helix of PPARγ. Binding of a PPAR ligand directly to the C-terminal AF-2 α-helical region appears to stabilize the charge clamp on the surface of the receptor, which is important for the recruitment of coactivator proteins to the receptor complex. GW9578, a ureido-thioisobutyric acid analog, has been identified as a PPARγ subtype-selective agonist. Brown, P. J.; Winegar, D. A.; Plunket, K. D.; Moore, L. B.; Lewis, M. C. et al., *J Med Chem* **1999**, *42*, 3785-3788.

Combinatorial chemistry and structure-based drug design have led to the identification of the subtype-selective PPARδ agonist GW501516. Oliver, W. R., Jr.; Shenk, J. L.; Snaith, M. R.; Russell, C. S.; Plunket, K. D. et al., *Proc Natl Acad Sci U S A* **2001**, *98*, 5306-5311. Recently, the ligand LG100754 has been found to exhibit little intrinsic transcriptional activity; rather, it appears to enhance the potency of PPAR ligands

for PPARγ-RXR. Forman, B. M., *J Biol Chem* 2002, *277*, 12503-12506. Finally, a number of naturally-occurring fatty acids and eicosanoid derivatives have been identified that bind and activate PPARγ at micromolar concentrations; and PGJ2 represents a prostaglandin that is widely used as a PPARγ agonist. Yu, K.; Bayona, W.; Kallen, C. B.; Harding, H. P.; Ravera, C. P. et al., *J Biol Chem* 1995, *270*, 23975-23983; Kliewer, S. A.; Lenhard, J. M.; Willson, T. M.; Patel, I.; Morris, D. C. et al., *Cell* 1995, *83*, 813-819.

Summary of the Invention

One aspect of the present invention relates to compounds with activity at a PPAR subtype. Another aspect of the invention relates to a method of identifying ligands using x-ray structural information for the PPARs. In certain embodiments, this method comprises using one or more of various molecular modeling approaches to identify candidate ligands selected from the group consisting of: 1) *in silico* screening of available chemical databases; 2) *de novo*/rational drug design in which a ligand will be created computationally in stages; and 3) design and *in silico* screening of virtual combinatorial libraries. In certain embodiments of the aforementioned method, a ligand is also assayed for PPAR isoform selectivity; ligands found to possess the desired specificity are then screened for their ability to block the growth of various human cancer cell lines.

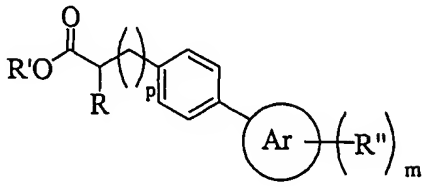
In certain embodiments, the present invention relates to a method, comprising:

1) identifying a novel PPARγ ligand using *de novo* drug design, combinatorial library generation, or virtual screening of chemical databases; chemically synthesizing the ligand;

2) assaying the ligand for PPAR selectivity and activity; based on the results of the assay and with the aid of molecular modeling; optionally conducting one or more additional rounds of chemical modification to optimize activity and/or selectivity; and

3) screening a ligand with an EC_{50} <1 μM in an assay for its ability to block cell proliferation in human cancer cell lines.

In certain embodiments, the present invention relates to a compound of formula I:



I

wherein

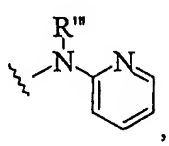
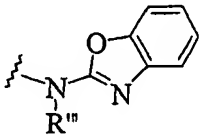
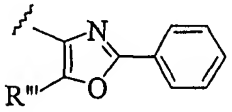
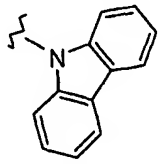
R' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, or an alkali metal cation;

R is H, C_1-C_6 alkyl, aryl, C_1-C_6 alkoxyl, C_4-C_{10} aryloxyl, -NHCO(C_1-C_6 alkyl), -NHCO(C_4-C_{10} aryl), -$NHSO_2$(C_1-C_6 alkyl), or -$NHSO_2$(C_4-C_{10} aryl);

Ar is a 5-10 membered aryl or heteroaryl ring, wherein the heteroaryl ring contains 1 to 3 heteroatoms selected from the group consisting of O, S, and N;

R" is -$(L)_nX$;

L, independently for each occurrence, is -CH_2-, O, N, or S;

X is C_1-C_6 alkoxyl, C_4-C_{10} aryloxyl, -CO_2(C_1-C_6 alkyl), -CO_2(C_4-C_{10} aryl), -C(O)NH(C_1-C_6 alkyl), -C(O)NH(C_4-C_{10} aryl),  ,  ,  , or  ;

R''' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, -SO_2(C_1-C_6 alkyl), -SO_2(C_4-C_{10} aryl), -C(O)(C_1-C_6 alkyl), or -C(O)(C_4-C_{10} aryl);

m is an integer from 0 to 5 inclusive;

n is an integer from 0 to 6 inclusive; and

p is an integer from 0 to 6.

In certain embodiments, the present invention relates to a compound of formula I and the attendant definitions, wherein R' is H.

In certain embodiments, the present invention relates to a compound of formula I and the attendant definitions, wherein Ar is selected from the group consisting of phenyl, thiophenyl, and pyrrolyl.

In certain embodiments, the present invention relates to a compound of formula I and the attendant definitions, wherein p is 1.

In certain embodiments, the present invention relates to a compound of formula I and the attendant definitions, wherein m is 1.

In certain embodiments, the present invention relates to a compound of formula I and the attendant definitions, wherein L is $-CH_2-$ and n is 1, 2, 3, or 4.

In certain embodiments, the present invention relates to a compound of formula I and the attendant definitions, wherein X is $-OCH_3$ or $-CO_2CH_3$.

In certain embodiments, the present invention relates to a compound of formula I and the attendant definitions, wherein R is selected from the group consisting of $-OCH_2CH_3$, $-NHCOCH_3$, and $-NHSO_2CH_3$.

In certain embodiments, the present invention relates to a compound of formula I and the attendant definitions, wherein R' is H; p is 1; m is 1; Ar is phenyl; R is $-OCH_2CH_3$; L is $-CH_2-$; n is 4; and X is $-OCH_3$.

In certain embodiments, the present invention relates to a compound of formula I and the attendant definitions, wherein R' is H; p is 1; m is 1; Ar is phenyl; R is $-NHCOCH_3$; L is $-CH_2-$; n is 4; and X is $-OCH_3$.

In certain embodiments, the present invention relates to a compound of formula I and the attendant definitions, wherein R' is H; p is 1; m is 1; Ar is phenyl; R is $-OCH_2CH_3$; L is $-CH_2-$; n is 3; and X is $-OCH_3$.

In certain embodiments, the present invention relates to a compound of formula I and the attendant definitions, wherein R' is H; p is 1; m is 1; Ar is phenyl; R is $-OCH_2CH_3$; L is $-CH_2-$; n is 2; and X is $-CO_2CH_3$.

In certain embodiments, the present invention relates to a compound of formula I and the attendant definitions, wherein R' is H; p is 1; m is 1; Ar is phenyl; R is $-NHSO_2CH_3$; L is $-CH_2-$; n is 2; and X is $-CO_2CH_3$.

In certain embodiments, the present invention relates to a compound of formula I and the attendant definitions, wherein R' is H; p is 1; m is 1; Ar is thiophenyl; R is $-OCH_2CH_3$; L is $-CH_2-$; n is 4; and X is $-OCH_3$.

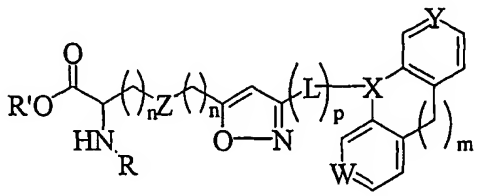
In certain embodiments, the present invention relates to a compound of formula I and the attendant definitions, wherein R' is H; p is 1; m is 1; Ar is pyrrolyl; R is $-OCH_2CH_3$; L is $-CH_2-$; n is 4; and X is $-OCH_3$.

In certain embodiments, the present invention relates to a compound of formula I and the attendant definitions, wherein R' is H; p is 1; m is 1; Ar is thiophenyl; R is OCH_2CH_3; L is $-CH_2-$; n is 2; and X is $-OCH_3$.

In certain embodiments, the present invention relates to a compound of formula I and the attendant definitions, wherein R' is H; p is 1; m is 1; Ar is pyrrolyl; R is $-OCH_2CH_3$; L is $-CH_2-$; n is 2; and L is $-OCH_3$.

In certain embodiments, the present invention relates to a compound of formula I and the attendant definitions, wherein R' is H; p is 1; m is 1; Ar is thiophenyl; R is $-OCH_2CH_3$; L is $-CH_2-$; n is 1; and X is $-OCH_3$.

In certain embodiments, the present invention relates to a compound of formula II:



II

wherein

R' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, or an alkali metal cation;

R is H, C_1-C_6 alkyl, C_4-C_{10} aryl, $-CO(C_1$-C_6 alkyl), $-CO(C_4$-C_{10} aryl), -CO(aralkyl), $-CO(aryl(C_2$-C_6 alkenyl)), $-CO(C_1$-C_6 alkyl)C(O)aryl, $-CO(C_2$-C_6 alkenyl)C(O)aryl, $-CO(C_2$-C_6 alkenyl)alkyl, $-CO_2(C_1$-C_6 alkyl)Oaralkyl, $-SO_2(C_1$-C_6 alkyl), $-SO_2(C_4$-C_{10} aryl), $-CO_2$(aralkyl), $-CO_2C(C_1$-C_6 alkyl)$_3$, aralkyl, or $-C(C_1$-C_6 alkyl)=CHC(O)aryl;

W is CH or N;

X is CH or N;

Y is CH or N;

Z is a bond, O, S, or NR;

L, independently for each occurrence, is $-CH_2-$, O, N, or S;

n independently for each occurrence, is an integer from 1 to 6 inclusive;

m is an integer from 0 to 2 inclusive; and

p is an integer from 1 to 6 inclusive.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein n is 1.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein L is $-CH_2-$ and p is 3, 4, 5 or 6.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein m is 0.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein Z is O.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein X is N.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein Y is CH.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein Y is N.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R is selected from the group consisting of H, CH_3, $-SO_2CH_3$, $-SO_2Ph$, $-COCH_3$, -COPh, $-CO_2CH_2Ph$, $-CO_2C(CH_3)_3$, $-CH_2Ph$, $-CH_2CH_2Ph$, $-CH_2CH_2CH_2Ph$, and -C(Me)=CHCOPh.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, L is $-CH_2-$, p is 5, Y is CH, and R is $-CH_3$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, L is $-CH_2-$, p is 5, Y is CH, and R is $-SO_2CH_3$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, L is $-CH_2-$, p is 3, Y is N, and R is $-CH_3$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, L is $-CH_2-$, p is 3, Y is N, and R is $-SO_2CH_3$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, L is $-CH_2-$, p is 3, Y is N, and R is $-SO_2Ph$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, L is $-CH_2-$, p is 3, Y is N, and R is $-COCH_3$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is $-CH_2-$, p is 3, and R is $-CO_2CH_2Ph$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is $-CH_2-$, p is 3, and R is $-CO_2C(CH_3)_3$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is $-CH_2-$, p is 3, and R is H.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is $-CH_2-$, p is 4, and R is $-SO_2CH_3$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is $-CH_2-$, p is 4, and R is $-CO_2C(CH_3)_3$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is $-CH_2-$, p is 4, and R is H.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is $-CH_2-$, p is 5, and R is $-CO_2C(CH_3)_3$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is $-CH_2-$, p is 5, and R is $-CH_2Ph$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is $-CH_2-$, p

is 5, and R is -CH_2CH_2Ph.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is -CH_2-, p is 5, and R is -$CH_2CH_2CH_2Ph$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is -CH_2-, p is 5, and R is H.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 2, n is 1, X is N, Y is CH, L is -CH_2-, p is 5, and R is -$CO_2C(CH_3)_3$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is -CH_2-, p is 5, and R is -COPh.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is -CH_2-, p is 5, and R is -CO_2CH_2Ph.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is -CH_2-, p is 5, and R is -$C(CH_3)$=CHCOPh.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is -CH_2-, p is 6, and R is -$CO_2C(CH_3)_3$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is -CH_2-, p is 5, and R is -CO(aralkyl).

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is -CH_2-, p is 5, and R is -$COCH_2$(4-fluorophenyl).

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein Z is O, R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is -CH_2-, p is 5, and R is -CO(aralkyl).

In certain embodiments, the present invention relates to a compound of formula II

and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-COCH_2CH_2Ph$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is -CO(aryl(C_2-C_6 alkenyl)).

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-COCH=CHPh$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein Z is O, R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is -CO(aryl(C_2-C_6 alkenyl)).

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is -CO(C_1-C_6 alkyl)C(O)aryl.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-COCH_2CH_2C(O)aryl$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-COCH_2CH_2C(O)Ph$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein Z is O, R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is -CO(C_1-C_6 alkyl)C(O)aryl.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein Z is O, R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-COCH_2CH_2C(O)aryl$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is -CO(C_2-C_6 alkenyl)C(O)aryl.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-COCH=CHC(O)aryl$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is -COCH=CHC(O)Ph.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein Z is O, R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is -CO(C_2-C_6 alkenyl)C(O)aryl.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein Z is O, R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is -COCH=CHC(O)aryl.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-CO(CH_2)_4CH_3$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is -CO(C_2-C_6 alkenyl)alkyl.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-COCH=CHCH=CHCH_3$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein Z is O, R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is -CO(C_2-C_6 alkenyl)alkyl.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-CO_2C(CH_3)_3$.

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-CO_2$(aralkyl).

In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-CO_2CH_2$-(2-chorophenyl).

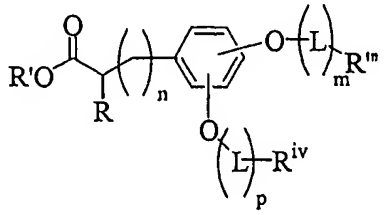
In certain embodiments, the present invention relates to a compound of formula II and the attendant definitions, wherein Z is O, R' is H, m is 0, n is 1, X is N, Y is CH, W is

CH, L is $-CH_2-$, p is 5, and R is $-CO_2$(aralkyl).

In certain embodiments, the present invention relates to a compound of formula **II** and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-CO_2CH_2$-(4-nitrophenyl) or $-CO_2CH_2$-(2-nitrophenyl).

In certain embodiments, the present invention relates to a compound of formula **II** and the attendant definitions, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-CO_2CH_2$-(2-nitro-4,5-dimethoxyphenyl).

In certain embodiments, the present invention relates to a compound of formula **III**:



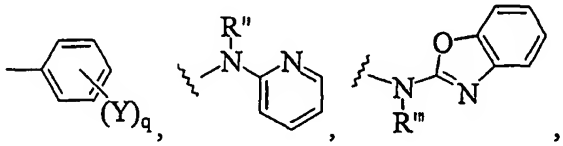
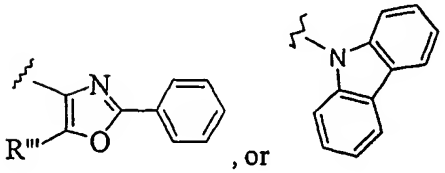
III

wherein

R' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, or an alkali metal cation;

R is H or NHR";

R" is H, C_1-C_6 alkyl, C_4-C_{10} aryl, $-SO_2(C_1$-C_6 alkyl), $-SO_2(C_4$-C_{10} aryl), $-C(O)(C_1$-C_6 alkyl), or $-C(O)(C_4$-C_{10} aryl);

R''' and R^{iv}, independently, are  ,  , or ;

Y is $-CF_3$ or $-(C_1$-C_6 alkyl)-O-$(C_1$-C_6 alkyl);

R''' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, $-SO_2(C_1$-C_6 alkyl), $-SO_2(C_4$-C_{10} aryl), $-C(O)(C_1$-C_6 alkyl), or $-C(O)(C_4$-C_{10} aryl); and

q is an integer from 0 to 5 inclusive;

L, independently for each occurrence, is $-CH_2-$, O, N, or S.

n is an integer from 0 to 5 inclusive;

m is, independently for each occurrence, an integer from 0 to 6 inclusive; and

p is an integer from 1 to 5 inclusive.

In certain embodiments, the present invention relates to a compound of formula III and the attendant definitions, wherein R' is H.

In certain embodiments, the present invention relates to a compound of formula III and the attendant definitions, wherein R is H.

In certain embodiments, the present invention relates to a compound of formula III and the attendant definitions, wherein R is NHR".

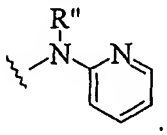
In certain embodiments, the present invention relates to a compound of formula III and the attendant definitions, wherein n is 1.

In certain embodiments, the present invention relates to a compound of formula III and the attendant definitions, wherein L is $-CH_2-$.

In certain embodiments, the present invention relates to a compound of formula III and the attendant definitions, wherein m is 0, 2, 3, or 4.

In certain embodiments, the present invention relates to a compound of formula III and the attendant definitions, wherein p is 2, 3, or 4.

In certain embodiments, the present invention relates to a compound of formula III and the attendant definitions, wherein R''' is Ph, p-$C_6H_4CF_3$, p-$C_6H_4CH_2CH_2OCH_3$, or



In certain embodiments, the present invention relates to a compound of formula III and the attendant definitions, wherein R^{iv} is -Ph, p-$C_6H_4CF_3$, or p-$C_6H_4CH_2CH_2OCH_3$.

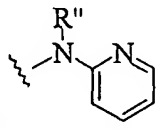
In certain embodiments, the present invention relates to a compound of formula III and the attendant definitions, wherein R' is H, R is H, n is 1, m is 0, L is $-CH_2-$, p is 2, R''' is Ph, and R^{iv} is Ph.

In certain embodiments, the present invention relates to a compound of formula III and the attendant definitions, wherein R' is H, R is H, n is 1, m is 0, L is $-CH_2-$, p is 2, R''' is p-$C_6H_4CF_3$, and R^{iv} is Ph.

In certain embodiments, the present invention relates to a compound of formula III and the attendant definitions, wherein R' is H, R is H, n is 1, m is 0, L is $-CH_2-$, p is 2, R''' is p-$C_6H_4CH_2CH_2OCH_3$, and R^{iv} is p-$C_6H_4CF_3$.

In certain embodiments, the present invention relates to a compound of formula III and the attendant definitions, wherein R' is H, R is H, n is 1, m is 0, L is $-CH_2-$, p is 2, R''' is p-$C_6H_4CH_2CH_2OCH_3$, and R^{iv} is o-$C_6H_4CF_3$.

In certain embodiments, the present invention relates to a compound of formula III and the attendant definitions, wherein R' is H, R is H, n is 1, m is 0, L is $-CH_2-$, p is 3, R''' is Ph, and R^{iv} is Ph.

In certain embodiments, the present invention relates to a compound of formula III and the attendant definitions, wherein R' is H, R is H, n is 1, m is 3, L is $-CH_2-$, p is 2, R''' is  , wherein R" is $-CH_3$, and R^{iv} is Ph.

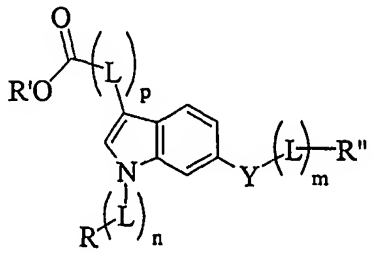
In certain embodiments, the present invention relates to a compound of formula III and the attendant definitions, wherein R' is H, R is NHR", R" is $-CH_3$, n is 1, p is 4, L is $-CH_2-$, m is 4, R''' is p-$C_6H_4CF_3$, and R^{iv} is p-$C_6H_4CF_3$.

In certain embodiments, the present invention relates to a compound of formula III and the attendant definitions, wherein R' is H, R is NHR", R" is $-CH_3$, n is 1, p is 3, L is $-CH_2-$, m is 3, R''' is p-$C_6H_4CF_3$, and R^{iv} is p-$C_6H_4CF_3$.

In certain embodiments, the present invention relates to a compound of formula III and the attendant definitions, wherein R' is H, R is NHR", R" is $-SO_2CH_3$, n is 1, p is 3, L is $-CH_2-$, m is 3, R''' is p-$C_6H_4CF_3$, and R^{iv} is p-$C_6H_4CF_3$.

In certain embodiments, the present invention relates to a compound of formula III and the attendant definitions, wherein R' is H, R is NHR", R" is $-CH_3$, n is 1, p is 2, L is $-CH_2-$, m is 2, R''' is p-$C_6H_4CF_3$, and R^{iv} is p-$C_6H_4CF_3$.

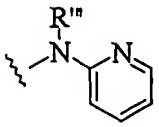
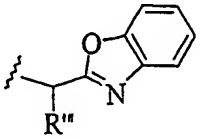
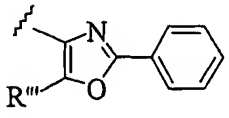
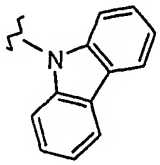
In certain embodiments, the present invention relates to a compound of formula IV:



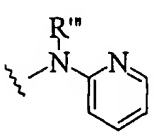
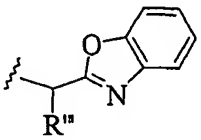
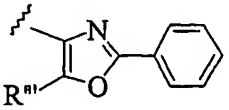
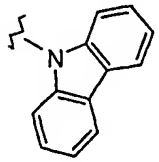
IV

wherein

R' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, or an alkali metal cation;

R is H, C_4-C_{10} aryl, -SO_2(C_1-C_6 alkyl), -SO_2(C_4-C_{10} aryl), -C(O)(C_1-C_6 alkyl), -C(O)(C_4-C_{10} aryl), -CO_2(C_1-C_6 alkyl), -CO_2(C_4-C_{10} aryl),  ,  ,  , or  ;

Y is O, S, or NR;

R" is H, C_4-C_{10} aryl,  ,  ,  , or  ;

R''' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, -SO_2(C_1-C_6 alkyl), -SO_2(C_4-C_{10} aryl), -C(O)(C_1-C_6 alkyl), or -C(O)(C_4-C_{10} aryl);

L, independently for each occurrence, is -CH_2-, O, N, or S;

n is an integer from 0 to 6 inclusive;

m is an integer from 1 to 6 inclusive; and

p is an integer from 0 to 6 inclusive.

In certain embodiments, the present invention relates to a compound of formula IV and the attendant definitions, wherein R' is H.

In certain embodiments, the present invention relates to a compound of formula IV and the attendant definitions, wherein L is -CH_2-.

In certain embodiments, the present invention relates to a compound of formula IV and the attendant definitions, wherein n is 3.

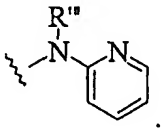
In certain embodiments, the present invention relates to a compound of formula IV and the attendant definitions, wherein m is 2.

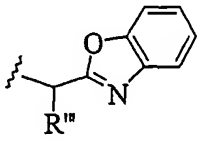
In certain embodiments, the present invention relates to a compound of formula IV and the attendant definitions, wherein p is 1.

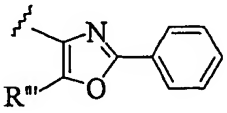
In certain embodiments, the present invention relates to a compound of formula IV and the attendant definitions, wherein R is Ph.

In certain embodiments, the present invention relates to a compound of formula IV and the attendant definitions, wherein Y is O.

In certain embodiments, the present invention relates to a compound of formula IV and the attendant definitions, wherein R" is Ph.

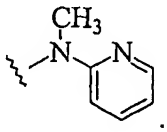
In certain embodiments, the present invention relates to a compound of formula IV and the attendant definitions, wherein R" is  .

In certain embodiments, the present invention relates to a compound of formula IV and the attendant definitions, wherein R" is  .

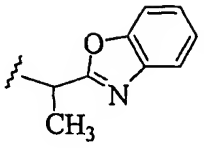
In certain embodiments, the present invention relates to a compound of formula IV and the attendant definitions, wherein R" is  .

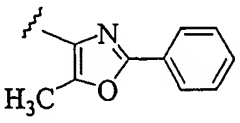
In certain embodiments, the present invention relates to a compound of formula IV and the attendant definitions, wherein R" is 2-naphtyl.

In certain embodiments, the present invention relates to a compound of formula IV and the attendant definitions, wherein R' is H, n is 3, m is 2, p is 1, L is $-CH_2-$, R is Ph, Y is O, and R" is Ph.

In certain embodiments, the present invention relates to a compound of formula IV and the attendant definitions, wherein R' is H, n is 3, m is 2, p is 1, L is $-CH_2-$, R is Ph, Y is O, and R" is  .

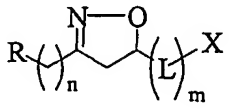
In certain embodiments, the present invention relates to a compound of formula IV and the attendant definitions, wherein R' is H, n is 3, m is 2, p is 1, L is $-CH_2-$, R is Ph, Y is

O, and R" is  .

In certain embodiments, the present invention relates to a compound of formula IV and the attendant definitions, wherein R' is H, n is 3, m is 2, p is 1, L is $-CH_2-$, R is Ph, Y is O, and R" is  .

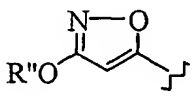
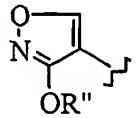
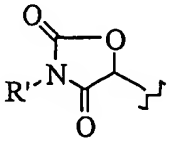
In certain embodiments, the present invention relates to a compound of formula IV and the attendant definitions, wherein R' is H, n is 3, m is 2, p is 1, L is $-CH_2-$, R is Ph, Y is O, and R" is 2-naphtyl.

In certain embodiments, the present invention relates to a compound of formula V:



V

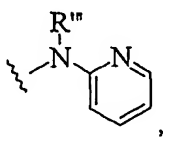
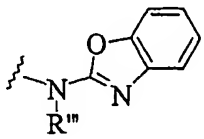
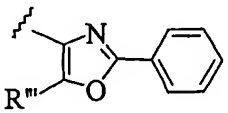
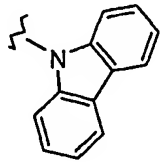
wherein

R is  ,  , or  ;

R' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, $-SO_2(C_1$-C_6 alkyl), $-SO_2(C_4$-C_{10} aryl), $-C(O)(C_1$-C_6 alkyl), or $-C(O)(C_4$-C_{10} aryl);

R'' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, or an alkali metal cation;

L, independently for each occurrence, is $-CH_2-$, O, N, or S;

X is  ,  ,  , or  ;

R''' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, $-SO_2(C_1$-C_6 alkyl), $-SO_2(C_4$-C_{10} aryl), $-C(O)(C_1$-C_6 alkyl), or $-C(O)(C_4$-C_{10} aryl);

m is an integer from 1 to 6 inclusive; and

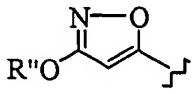
n is an integer from 1 to 6 inclusive.

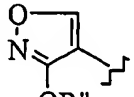
In certain embodiments, the present invention relates to a compound of formula V

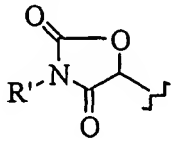
and the attendant definitions, wherein R" is H.

In certain embodiments, the present invention relates to a compound of formula V and the attendant definitions, wherein R' is $-CH_3$.

In certain embodiments, the present invention relates to a compound of formula V and the attendant definitions, wherein n is 1.

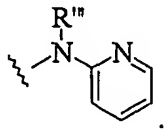
In certain embodiments, the present invention relates to a compound of formula V and the attendant definitions, wherein R is  .

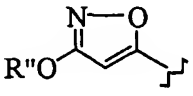
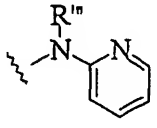
In certain embodiments, the present invention relates to a compound of formula V and the attendant definitions, wherein R is  .

In certain embodiments, the present invention relates to a compound of formula V and the attendant definitions, wherein R is  .

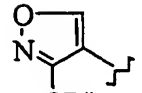
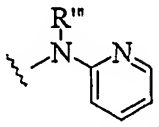
In certain embodiments, the present invention relates to a compound of formula V and the attendant definitions, wherein L is $-CH_2-$.

In certain embodiments, the present invention relates to a compound of formula V and the attendant definitions, wherein m is 3.

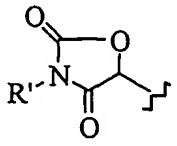
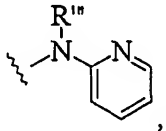
In certain embodiments, the present invention relates to a compound of formula V and the attendant definitions, wherein X is  .

In certain embodiments, the present invention relates to a compound of formula V and the attendant definitions, wherein R" is H, n is 1, R' is $-CH_3$, R is  , L is $-CH_2-$, m is 3, X is  , and R''' is $-CH_3$.

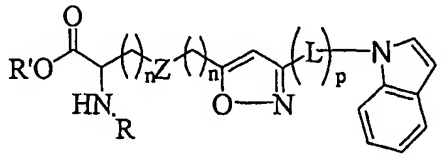
In certain embodiments, the present invention relates to a compound of formula V

and the attendant definitions, wherein R" is H, n is 1, R' is -CH_3, R is  , L is -CH_2-, m is 3, X is  , and R''' is -CH_3.

In certain embodiments, the present invention relates to a compound of formula **V**

and the attendant definitions, wherein R" is H, n is 1, R' is -CH_3, R is  , L is -CH_2-, m is 3, X is  , and R''' is -CH_3.

In certain embodiments, the present invention relates to a compound of formula **VI**:



VI

wherein

R' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, or an alkali metal cation;

R is H, C_1-C_6 alkyl, C_4-C_{10} aryl, -CO(C_1-C_6 alkyl), -CO(C_4-C_{10} aryl), -CO(aralkyl), -CO(aryl(C_2-C_6 alkenyl)), -CO(C_1-C_6 alkyl)C(O)aryl, -CO(C_2-C_6 alkenyl)C(O)aryl, -CO(C_2-C_6 alkenyl)alkyl, -CO_2(C_1-C_6 alkyl)Oaralkyl, -SO_2(C_1-C_6 alkyl), -SO_2(C_4-C_{10} aryl), -CO_2(aralkyl), -CO_2C(C_1-C_6 alkyl)$_3$, aralkyl, or -C(C_1-C_6 alkyl)=CHC(O)aryl;

Z is a bond, O, S, or NR;

L, independently for each occurrence, is -CH_2-, O, N, or S;

n independently for each occurrence, is an integer from 1 to 6 inclusive; and

p is an integer from 1 to 6 inclusive.

In certain embodiments, the present invention relates to a compound of formula **VI** and the attendant definitions, wherein Z is O.

In certain embodiments, the present invention relates to a compound of formula VI and the attendant definitions, wherein R' is H.

In certain embodiments, the present invention relates to a compound of formula VI and the attendant definitions, wherein n is 1.

In certain embodiments, the present invention relates to a compound of formula VI and the attendant definitions, wherein L is $-CH_2-$ and p is 4, 5 or 6.

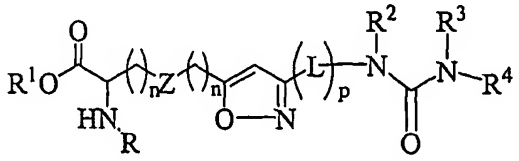
In certain embodiments, the present invention relates to a compound of formula VI and the attendant definitions, wherein R is selected from the group consisting of H, CH_3, $-SO_2CH_3$, $-SO_2Ph$, $-COCH_3$, $-COPh$, $-CO_2CH_2Ph$, $-CO_2C(CH_3)_3$, $-CH_2Ph$, $-CH_2CH_2Ph$, $-CH_2CH_2CH_2Ph$, and $-C(Me)=CHCOPh$.

In certain embodiments, the present invention relates to a compound of formula VI and the attendant definitions, wherein Z is O, and R is selected from the group consisting of $-COCH_3$, $-COPh$, $-CO_2CH_2Ph$, $-CO_2C(CH_3)_3$, $-CH_2Ph$, $-CH_2CH_2Ph$, $-CH_2CH_2CH_2Ph$, and $-C(Me)=CHCOPh$.

In certain embodiments, the present invention relates to a compound of formula VI and the attendant definitions, wherein R' is H, n is 1, L is $-CH_2-$, and p is 5.

In certain embodiments, the present invention relates to a compound of formula VI and the attendant definitions, wherein Z is O, R' is H, n is 1, L is $-CH_2-$, p is 5, and R is $-CO_2CH_2Ph$.

In certain embodiments, the present invention relates to a compound of formula VII:



VII

wherein

R is H, C_1-C_6 alkyl, C_4-C_{10} aryl, $-CO(C_1$-C_6 alkyl), $-CO(C_4$-C_{10} aryl), -CO(aralkyl), $-CO(aryl(C_2$-C_6 alkenyl)), $-CO(C_1$-C_6 alkyl)C(O)aryl, $-CO(C_2$-C_6 alkenyl)C(O)aryl, $-CO(C_2$-C_6 alkenyl)alkyl, $-CO_2(C_1$-C_6 alkyl)Oaralkyl, $-SO_2(C_1$-C_6 alkyl), $-SO_2(C_4$-C_{10} aryl), $-CO_2$(aralkyl), $-CO_2C(C_1$-C_6 alkyl)$_3$, aralkyl, or $-C(C_1$-C_6 alkyl)=CHC(O)aryl;

R^1 is H, C_1-C_6 alkyl, C_4-C_{10} aryl, or an alkali metal cation;

R^2 is H, alkyl, aryl, or aralkyl;

R^3 is H, alkyl, aryl, or aralkyl;

R^4 is aryl or aralkyl;

Z is a bond, O, S, or NR;

L, independently for each occurrence, is $-CH_2-$, O, N, or S;

n independently for each occurrence, is an integer from 1 to 6 inclusive; and

p is an integer from 1 to 6 inclusive.

In certain embodiments, the present invention relates to a compound of formula **VII** and the attendant definitions, wherein Z is O.

In certain embodiments, the present invention relates to a compound of formula **VII** and the attendant definitions, wherein R^1 is H.

In certain embodiments, the present invention relates to a compound of formula **VII** and the attendant definitions, wherein n is 1.

In certain embodiments, the present invention relates to a compound of formula **VII** and the attendant definitions, wherein L is $-CH_2-$ and p is 3, 4, or 5.

In certain embodiments, the present invention relates to a compound of formula **VII** and the attendant definitions, wherein R is selected from the group consisting of H, CH_3, $-SO_2CH_3$, $-SO_2Ph$, $-COCH_3$, -COPh, $-CO_2CH_2Ph$, $-CO_2C(CH_3)_3$, $-CH_2Ph$, $-CH_2CH_2Ph$, $-CH_2CH_2CH_2Ph$, and -C(Me)=CHCOPh.

In certain embodiments, the present invention relates to a compound of formula **VII** and the attendant definitions, wherein Z is O, and R is selected from the group consisting of $-COCH_3$, -COPh, $-CO_2CH_2Ph$, $-CO_2C(CH_3)_3$, $-CH_2Ph$, $-CH_2CH_2Ph$, $-CH_2CH_2CH_2Ph$, and -C(Me)=CHCOPh.

In certain embodiments, the present invention relates to a compound of formula **VII** and the attendant definitions, wherein R^1 is H, n is 1, L is $-CH_2-$, p is 4, and R is $-CO_2CH_2Ph$.

In certain embodiments, the present invention relates to a compound of formula **VII** and the attendant definitions, wherein R^2 is alkyl and R^3 is H.

In certain embodiments, the present invention relates to a compound of formula **VII** and the attendant definitions, wherein R^2 is alkyl and R^3 is H, and R^4 is aryl.

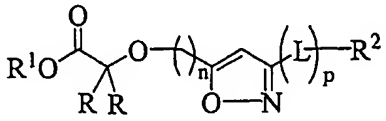
In certain embodiments, the present invention relates to a compound of formula **VII** and the attendant definitions, wherein R^2 is alkyl and R^3 is H, and R^4 is phenyl or halophenyl.

In certain embodiments, the present invention relates to a compound of formula **VII** and the attendant definitions, wherein R^1 is H, n is 1, L is $-CH_2-$, p is 4, R is $-CO_2CH_2Ph$, R^2 is alkyl and R^3 is H, and R^4 is aryl.

In certain embodiments, the present invention relates to a compound of formula **VII** and the attendant definitions, wherein Z is O, R^1 is H, n is 1, L is $-CH_2-$, p is 4, R is $-CO_2CH_2Ph$, R^2 is heptyl, R^3 is H, and R^4 is 2,4-difluorophenyl.

In certain embodiments, the present invention relates to a compound of formula **VII** and the attendant definitions, wherein Z is O, R^1 is H, n is 1, L is $-CH_2-$, p is 4, R is $-CO_2CH_2Ph$, R^2 is heptyl, R^3 is H, and R^4 is phenyl.

In certain embodiments, the present invention relates to a compound of formula **VIII**:



VIII

wherein

R is H or C_1-C_6 alkyl;

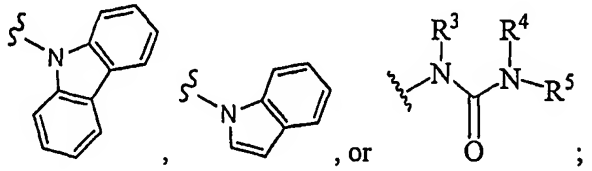
R^1 is H, C_1-C_6 alkyl, C_4-C_{10} aryl, or an alkali metal cation;

L, independently for each occurrence, is $-CH_2-$, O, N, or S.

n independently for each occurrence, is an integer from 1 to 6 inclusive;

p is an integer from 1 to 6 inclusive; and

R^2 is



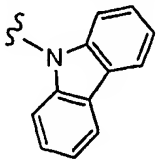
wherein R^3 is H or alkyl; R^4 is H or alkyl; and R^5 is aryl.

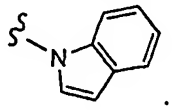
In certain embodiments, the present invention relates to a compound of formula **VIII** and the attendant definitions, wherein R^1 is H.

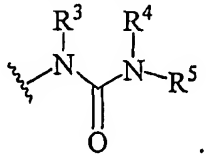
In certain embodiments, the present invention relates to a compound of formula **VIII** and the attendant definitions, wherein n is 1.

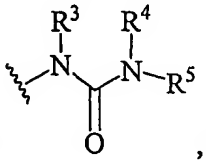
In certain embodiments, the present invention relates to a compound of formula VIII and the attendant definitions, wherein L is $-CH_2-$ and p is 3, 4, or 5.

In certain embodiments, the present invention relates to a compound of formula VIII and the attendant definitions, wherein R is methyl.

In certain embodiments, the present invention relates to a compound of formula VIII and the attendant definitions, wherein R^1 is H, R is methyl, n is 1, L is $-CH_2-$, p is 5, and R^2 is  .

In certain embodiments, the present invention relates to a compound of formula VIII and the attendant definitions, wherein R^1 is H, R is methyl, n is 1, L is $-CH_2-$, p is 5, and R^2 is  .

In certain embodiments, the present invention relates to a compound of formula VIII and the attendant definitions, wherein R^1 is H, R is methyl, n is 1, L is $-CH_2-$, p is 4, and R^2 is  .

In certain embodiments, the present invention relates to a compound of formula VIII and the attendant definitions, wherein R^1 is H, R is methyl, n is 1, L is $-CH_2-$, p is 4, R^2 is  , R^3 is heptyl, R^4 is H, and R^5 is 2,4-difluorophenyl.

In certain embodiments, the present invention relates to a compound of formula I, II, III, IV, V, VI, VII, or VIII, wherein said compound is a single stereoisomer.

In certain embodiments, the present invention relates to a pharmaceutical composition, comprising a compound of formula I, II, III, IV, V, VI, VII, or VIII; and a pharmaceutically acceptable excipient.

In certain embodiments, the present invention relates to a method of modulating a PPAR comprising contacting the PPAR with a compound of formula I, II, III, IV, V, VI, VII, or VIII.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with cancer comprising administering to the mammal a therapeutically effective amount of a compound of formula I, II, III, IV, V, VI, VII, or VIII.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with breast cancer comprising administering to the mammal a therapeutically effective amount of a compound of formula I, II, III, IV, V, VI, VII, or VIII.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with prostate cancer comprising administering to the mammal a therapeutically effective amount of a compound of formula I, II, III, IV, V, VI, VII, or VIII.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with stomach cancer comprising administering to the mammal a therapeutically effective amount of a compound of formula I, II, III, IV, V, VI, VII, or VIII.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with lung cancer comprising administering to the mammal a therapeutically effective amount of a compound of formula I, II, III, IV, V, VI, VII, or VIII.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with colon cancer comprising administering to the mammal a therapeutically effective amount of a compound of formula I, II, III, IV, V, VI, VII, or VIII.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with pancreatic cancer comprising administering to the mammal a therapeutically effective amount of a compound of formula I, II, III, IV, V, VI, VII, or VIII.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with an inflammatory condition or disease, comprising administering to

the mammal a therapeutically effective amount of a compound of formula **I, II, III, IV, V, VI, VII,** or **VIII**.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with non-insulin-dependent (type II) diabetes, comprising administering to the mammal a therapeutically effective amount of a compound of formula **I, II, III, IV, V, VI, VII,** or **VIII**.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with a dyslipidemia, comprising administering to the mammal a therapeutically effective amount of a compound of formula **I, II, III, IV, V, VI, VII,** or **VIII**.

In certain embodiments, the present invention relates to a method of identifying a compound having PPAR selectivity and activity, comprising *de novo* drug design, combinatorial library generation, or virtual screening of chemical databases.

In another embodiment, the method of identifying compounds having PPAR selectivity and activity further comprises synthesizing a chemical compound originating from the *de novo* design approach.

In another embodiment, the method of identifying compounds having PPAR selectivity and activity further comprises conducting a round of chemical modification to enhance activity and/or selectivity based on assays for PPAR selectivity and activity.

In another embodiment, the method of identifying compounds having PPAR selectivity and activity further comprises screening a compound for its ability to block cell proliferation in human cancer cell lines.

In another embodiment, the method of identifying compounds having PPAR selectivity and activity optionally comprises further modifying a ligand to enhance its cell permeability.

In certain embodiments, the present invention relates to a method of modulating a PPAR, comprising contacting the PPAR with a compound of formula **I, II, III, IV,** or **V**.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with cancer, comprising administering to the mammal a therapeutically effective amount of a compound of formula **I, II, III, IV,** or **V**.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with breast cancer, comprising administering to the mammal a

therapeutically effective amount of a compound of formula I, II, III, IV, or V.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with prostate cancer, comprising administering to the mammal a therapeutically effective amount of a compound of formula I, II, III, IV, or V.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with stomach cancer, comprising administering to the mammal a therapeutically effective amount of a compound of formula I, II, III, IV, or V.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with lung cancer, comprising administering to the mammal a therapeutically effective amount of a compound of formula I, II, III, IV, or V.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with colon cancer, comprising administering to the mammal a therapeutically effective amount of a compound of formula I, II, III, IV, or V.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with pancreatic cancer, comprising administering to the mammal a therapeutically effective amount of a compound of formula I, II, III, IV, or V.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with an inflammatory condition or disease, comprising administering to the mammal a therapeutically effective amount of a compound of formula I, II, III, IV, or V.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with non-insulin-dependent (type II) diabetes, comprising administering to the mammal a therapeutically effective amount of a compound of formula I, II, III, IV, or V.

In certain embodiments, the present invention relates to a method of treating a mammal afflicted with a dyslipidemia, comprising administering to the mammal a therapeutically effective amount of a compound of formula I, II, III, IV, or V.

Brief Description of the Figures

Figure 1 depicts eight compounds that are active at a PPAR.

Figure 2 depicts five compounds that are active at PPARγ.

Figure 3 depicts a 3D search strategy using the 3D UNITY database module in Sybyl.

Figure 4 depicts a 3D search strategy using the 3D UNITY database module in Sybyl.

Figure 5 depicts four classes of PPAR agonists designed using a *de novo*/rational design method of the present invention.

Figure 6 depicts a combinatorial library based on a 2,4-dihydroxyphenylalkanoic acid core.

Figure 7 depicts an isoxazolyl-based ligand of the present invention, wherein sectors are labeled "core" and "sidechain"; these terms are also used in reference to the combinatorial libraries of the present invention.

Figure 8 depicts various combinatorial libraries of the present invention.

Figure 9 depicts a method for the optimization of sidechains of compounds of the present invention and for the discovery of additional compounds of the present invention.

Figure 10 depicts a number of modifications that may be made to a compound of the present invention.

Figure 11 depicts graphically the agonist activities of 11 isoxazolyl-based ligands, ZW-40 to ZW-50 at PPARα. The Figure also depicts graphically the agonist activity of the known PPARα ligand, WY14643.

Figure 12 depicts graphically the agonist activities of six isoxazolyl-based ligands, ZW-41, and ZW-50 to ZW-55 at PPARα. The Figure also depicts graphically the agonist activities of three known PPAR ligands, WY14643 (PPARα), GW7845 (PPARγ) and L165041 (PPARδ), and one RXR ligand, LG101305.

Figure 13 depicts graphically the agonist activities of 11 isoxazolyl-based ligands, ZW-40 to ZW-50 at PPARγ. The Figure also depicts graphically the agonist activity of the known PPARγ ligand, GW7845.

Figure 14 depicts graphically the agonist activities of six isoxazolyl-based ligands, ZW-41, and ZW-51 to ZW-55 at PPARγ. The Figure depicts graphically the agonist activities of three known PPAR ligands, WY14643 (PPARα), GW7845 (PPARγ) and L165041 (PPARδ), and one RXR ligand, LG101305.

Figure 15 depicts graphically the agonist activity dose-response of three isoxazolyl-based ligands, ZW-41, ZW-53 and ZW-55 at PPARα. The Figure also depicts graphically the agonist activity of the known PPARα ligand, WY14643.

Figure 16 depicts graphically the agonist activity dose-response of WY14643, ZW-

53 and ZW-64 at PPARα.

Detailed Description of the Invention

The peroxisome proliferator-activated receptor (PPAR) subfamily of nuclear receptors are ligand-dependent transcription factors that regulate the expression of genes involved in lipid, glucose and energy homeostasis. Recent evidence indicates that pharmacological activation of PPARγ and inhibition of PPARδ has chemopreventive and antitumor effects. PPARγ agonists induce differentiation, inhibit the growth of established tumor cells *in vitro* and *in vivo*, and have chemopreventive effects in animal models. PPARγ suppresses Bcl-2 expression in prostate and colon cancers, activates the $p27^{Kip1}$ and $p21^{Cip1}$ inhibitors of cyclin A, D and E-dependent protein kinase2 and transactivates the tumor suppressor gene, *PTEN*. PPAR ligands also have additional advantageous biological properties. PPARα and PPARγ activation produce antiinflammatory and differentiating activity and protect against the oxidative damage associated with aging. In contrast, the upregulation of PPARδ may be a contributing factor in colorectal carcinogenesis since its expression is induced by an activated β-catenin/TCF pathway resulting from loss-of-function mutations in the APC tumor suppressor gene, a risk factor associated with colon cancer.

Because of the association between PPARγ activation and the inhibition of cancer progression, unique ligands that target this receptor should constitute a novel strategy for the development of anticancer agents that function at the transcriptional level. Classes of agents that act primarily as ligands for PPARγ include the thiazolidinediones, α-alkoxy-β-phenylpropanoic acids, and tyrosine-based agonists. Such agents have been investigated primarily for their antihyperglycemic and antihyperlipidemic activity, and the thiazolidenediones pioglitazone and rosiglitazone are presently used for the treatment of non-insulin-dependent diabetes. At the structural level, the PPARγ binding pocket is sufficiently large that it is able to accommodate ligands of diverse structure.

Definitions

For convenience, certain terms employed in the specification, examples, and appended claims are collected here.

The articles "a" and "an" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The term "ED_{50}" means the dose of a drug which produces 50% of its maximum response or effect. Alternatively, the dose which produces a pre-determined response in 50% of test subjects or preparations.

The term "LD_{50}" means the dose of a drug which is lethal in 50% of test subjects.

The term "therapeutic index" refers to the therapeutic index of a drug defined as LD_{50}/ED_{50}.

The term "structure-activity relationship (SAR)" refers to the way in which altering the molecular structure of drugs alters their interaction with a receptor, enzyme, etc.

The term "agonist" refers to a compound that mimics the action of natural transmitter or, when the natural transmitter is not known, causes changes at the receptor complex in the absence of other receptor ligands.

The term "antagonist" refers to a compound that binds to a receptor site, but does not cause any physiological changes unless another receptor ligand is present.

The term "inverse agonist" refers to a compound that binds to a constitutively active receptor site and reduces its physiological function.

The term "competitive antagonist" refers to a compound that binds to a receptor site; its effects can be overcome by increased concentration of the agonist.

The term "partial agonist" refers to a compound that binds to a receptor site but does not produce the maximal effect regardless of its concentration.

The term "ligand" refers to a compound that binds at the receptor site.

The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are boron, nitrogen, oxygen, phosphorus, sulfur and selenium.

The term "alkyl" refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In preferred embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C_1-C_{30} for straight chain, C_3-C_{30} for branched chain), and more preferably 20 or fewer. Likewise, preferred cycloalkyls have from 3-10 carbon atoms in their ring structure, and more preferably have 5, 6 or 7 carbons in the ring structure.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to ten carbons, more

preferably from one to six carbon atoms in its backbone structure. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths. Preferred alkyl groups are lower alkyls. In preferred embodiments, a substituent designated herein as alkyl is a lower alkyl.

The term "aralkyl", as used herein, refers to an alkyl group substituted with an aryl group (e.g., an aromatic or heteroaromatic group).

The terms "alkenyl" and "alkynyl" refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

The term "aryl" as used herein includes 5-, 6- and 7-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles" or "heteroaromatics." The aromatic ring can be substituted at one or more ring positions with such substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, $-CF_3$, -CN, or the like. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls.

The terms *ortho*, *meta* and *para* apply to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and *ortho*-dimethylbenzene are synonymous.

The terms "heterocyclyl" or "heterocyclic group" refer to 3- to 10-membered ring structures, more preferably 3- to 7-membered rings, whose ring structures include one to four heteroatoms. Heterocycles can also be polycycles. Heterocyclyl groups include, for example, azetidine, azepine, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline,

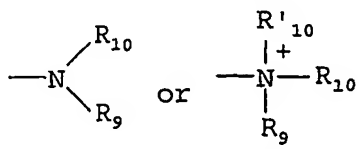
pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring can be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like.

The terms "polycyclyl" or "polycyclic group" refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like.

The term "carbocycle", as used herein, refers to an aromatic or non-aromatic ring in which each atom of the ring is carbon.

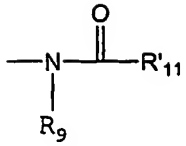
As used herein, the term "nitro" means $-NO_2$; the term "halogen" designates -F, -Cl, -Br or -I; the term "sulfhydryl" means -SH; the term "hydroxyl" means -OH; and the term "sulfonyl" means $-SO_2-$.

The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety that can be represented by the general formula:



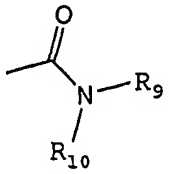
wherein R_9, R_{10} and R'_{10} each independently represent a group permitted by the rules of valence.

The term "acylamino" is art-recognized and refers to a moiety that can be represented by the general formula:



wherein R_9 is as defined above, and R'_{11} represents a hydrogen, an alkyl, an alkenyl or $-(CH_2)_m-R_8$, where m and R_8 are as defined above.

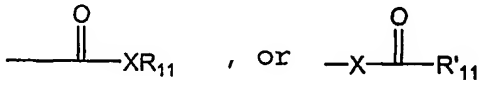
The term "amido" is art recognized as an amino-substituted carbonyl and includes a moiety that can be represented by the general formula:



wherein R_9, R_{10} are as defined above. Preferred embodiments of the amide will not include imides which may be unstable.

The term "alkylthio" refers to an alkyl group, as defined above, having a sulfur radical attached thereto. In preferred embodiments, the "alkylthio" moiety is represented by one of -S-alkyl, -S-alkenyl, -S-alkynyl, and $-S-(CH_2)_m-R_8$, wherein m and R_8 are defined above. Representative alkylthio groups include methylthio, ethyl thio, and the like.

The term "carbonyl" is art recognized and includes such moieties as can be represented by the general formula:



wherein X is a bond or represents an oxygen or a sulfur, and R_{11} represents a hydrogen, an alkyl, an alkenyl, $-(CH_2)_m-R_8$ or a pharmaceutically acceptable salt, R'_{11} represents a hydrogen, an alkyl, an alkenyl or $-(CH_2)_m-R_8$, where m and R_8 are as defined above. Where X is an oxygen and R_{11} or R'_{11} is not hydrogen, the formula represents an "ester". Where X is an oxygen, and R_{11} is as defined above, the moiety is referred to herein as a carboxyl group, and particularly when R_{11} is a hydrogen, the formula represents a "carboxylic acid". Where X is an oxygen, and R'_{11} is hydrogen, the formula represents a "formate". In general, where the oxygen atom of the above formula is replaced by sulfur, the formula represents a "thiolcarbonyl" group. Where X is a sulfur and R_{11} or R'_{11} is not hydrogen, the formula represents a "thiolester." Where X is a sulfur and R_{11} is hydrogen,

the formula represents a "thiolcarboxylic acid." Where X is a sulfur and R_{11}' is hydrogen, the formula represents a "thiolformate." On the other hand, where X is a bond, and R_{11} is not hydrogen, the above formula represents a "ketone" group. Where X is a bond, and R_{11} is hydrogen, the above formula represents an "aldehyde" group.

The terms "alkoxyl" or "alkoxy" as used herein refers to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as can be represented by one of -O-alkyl, -O-alkenyl, -O-alkynyl, $-O-(CH_2)_m-R_8$, where m and R_8 are described above.

The abbreviations Me, Et, Ph, Tf, Nf, Ts, Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, *p*-toluenesulfonyl and methanesulfonyl, respectively. A more comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the *Journal of Organic Chemistry*; this list is typically presented in a table entitled Standard List of Abbreviations. The abbreviations contained in said list, and all abbreviations utilized by organic chemists of ordinary skill in the art are hereby incorporated by reference.

Analogous substitutions can be made to alkenyl and alkynyl groups to produce, for example, aminoalkenyls, aminoalkynyls, amidoalkenyls, amidoalkynyls, iminoalkenyls, iminoalkynyls, thioalkenyls, thioalkynyls, carbonyl-substituted alkenyls or alkynyls.

As used herein, the definition of each expression, e.g. alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for

example, those described herein above. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds.

The phrase "protecting group" as used herein means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. The field of protecting group chemistry has been reviewed (Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991).

Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, it may be isolated using chiral chromatography methods, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Contemplated equivalents of the compounds described above include compounds which otherwise correspond thereto, and which have the same general properties thereof (e.g., functioning as analgesics), wherein one or more simple variations of substituents are made which do not adversely affect the efficacy of the compound in binding to opioid

receptors. In general, the compounds of the present invention may be prepared by the methods illustrated in the general reaction schemes as, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are in themselves known, but are not mentioned here.

For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.

PPAR Structural Information

One aspect of the present invention relates to generating new PPARγ ligands using the structural information available from the x-ray structure of the PPARγ ligand-binding domain in complexed with rosiglitazone. The ligand-binding site in apo-PPARγ is relatively large (~1300 $Å^3$) and Y-shaped extending from the C-terminal α-helix (known as AF-2) to the β-sheet between helices 3 and 6. Rosiglitazone binds in a U-shaped conformation, and occupies only 40% of the ligand-binding site. It engages in a number of specific H-bond interactions with His^{449}, Tyr^{473}, His^{323}, Ser^{289} and Gln^{286}. Because of the size of the ligand-binding pocket, PPARγ is capable of binding a number of structurally diverse ligands including the thiazolidinediones, α-alkoxy-β-phenylpropanoic acids, and tyrosine-based agonists. The size of this binding pocket also strongly suggests that it should be possible to design or identify new ligands with altered binding characteristics and modified receptor pharmacology.

The overall structure of the ligand-binding domain of PPARδ is similar to that of PPARγ. However, the ligand-binding pockets of PPARα and PPARγ are significantly larger than the PPARδ binding pocket, for the latter shows a narrowing of the pocket adjacent to the AF-2 helix. The shape of the pocket differs somewhat due to the differences in the residues lining the ligand-binding site. The TZDs and the L-tyrosine-based agonists show little if any binding to PPARδ, for their acidic head groups appear to be too large to fit within the narrow PPARδ pocket. Most of the ligands for PPARδ are either of low affinity or lack selectivity, but recently the compound GW501516 was identified as a selective PPARδ agonist. Oliver, W. R., Jr.; Shenk, J. L.; Snaith, M. R.; Russell, C. S.; Plunket, K. D. et al., *Proc Natl Acad Sci U S A* **2001**, *98*, 5306-5311.

As noted, the ligand-binding pockets of PPARα and PPARγ are close in size and

shape in comparison to PPARδ. The substitution of a single amino acid, Tyr^{314} in PPARα for His^{323} in PPARγ appears to be the major determinant of selectivity between these two subtypes based upon a comparison of x-ray complexes. Xu, H. E.; Lambert, M. H.; Montana, V. G.; Plunket, K. D.; Moore, L. B. et al., *Proc Natl Acad Sci U S A* **2001**, *98*, 13919-13924. Point mutation studies support the idea that these single amino acids are in fact responsible for determining the subtype selectivity of farglitazar (GW262570), which is 1000-fold selective for PPARγ over PPARα. The PPARα pocket is also more lipophilic and less solvent exposed than the PPARδ and PPARγ pockets.

With the wealth of x-ray information available for the PPARs, it is possible to use this together with molecular modeling methods to effect the design of new PPAR ligands. It is worth noting that a number of successful examples of structure-based drug design have been reported; for example, the discovery of an HIV-1 integrase inhibitor, FKBP-12 ligand, Factor Xa inhibitor, COX-2 inhibitor, and DNA gyrase inhibitor. Nicklaus, M. C.; Neamati, N.; Hong, H.; Mazumder, A.; Sunder, S. et al., *J Med Chem* **1997**, *40*, 920-929; Babine, R. E.; Bleckman, T. M.; Kissinger, C. R.; Showalter, R.; Pelletier, L. A. et al., *Bioorganic & Medicinal Chemistry Letters* **1995**, *5*, 1719-1724; Maduskuie, T. P., Jr.; McNamara, K. J.; Ru, Y.; Knabb, R. M.; Stouten, P. F., *J Med Chem* **1998**, *41*, 53-62; Stewart, K. D.; Loren, S.; Frey, L.; Otis, E.; Klinghofer, V. et al., *Bioorg Med Chem Lett* **1998**, *8*, 529-534; Boehm, H. J.; Boehringer, M.; Bur, D.; Gmuender, H.; Huber, W. et al., *J Med Chem* **2000**, *43*, 2664-2674.

Overview of Structure-Based Drug Design

In most cases, the methods for structure-based drug design are based on computational descriptions of a binding site -- for example, the coordinates of atoms or pharmacophores -- as well as techniques to search for the configurational and conformational space of a candidate molecule in the binding site to evaluate potential energy and/or scoring of binding affinity. The modeling methods that are used can be classified into three general categories: 3D database search; *de novo* drug design; and virtual combinatorial library approach. Desjarlais, R. L., *Practical Application of Computer-aided Drug Design*; Marcel Dekker: New York, 1997; pp 73-104; Good, A. C. M. J. S., *Reviews in Computational Chemistry*; VCH Publishers: New York, 1996; pp 67-117; Murcko, M. A., *Practical Application of Computer-aided Drug Design*; Marcel Dekker: New York, 1997; pp 304-354.

In the case of the 3D database search, programs such as DOCK, Catalyst, and UNITY take a molecule from a known compound database and attempt to position it in the active site of a receptor or pharmacophore model. Kuntz, I. D.; Blaney, J. M.; Oatley, S. J.; Langridge, R.; Ferrin, T. E., *J Mol Biol* 1982, *161*, 269-288; Catalyst *Catalyst*; Accelrys Inc.: San Diego; Sybyl *SYBYL®*; 6.8 ed.; Tripos Inc.: St. Louis; Unity *UNITY®*; 4.3 ed.; Tripos Inc.: St. Louis. The three-dimensional database search is widely accepted, as the target compounds are either found in commercial catalogs or are available synthetically. However, it is important to take note of some limitations that are inherent in most 3D database search programs: (1) the number of conformations calculated for each ligand is often insufficient; (2) the pharmacophore model used for the 3D query is usually simplified to speed up the search; (3) some functional groups exist in their ionic form under physiological conditions (pH 7.4), whereas the 3D database search programs often use the neutral forms of the ligands studied; and (4) novel structures cannot be obtained in cases where commercial or public databases (e.g., ACD or NCI) are employed.

On the other hand, *de novo* design programs, such as LeapFrog, CONCERTS, PRO-LIGAND, and LUDI, sequentially build up structures that are predicted to fit the active site of the receptor. Leapfrog *Leapfrog*; 6.8 ed.; Tripos Inc.: St. Louis; Pearlman, D. A.; Murcko, M. A., *J Med Chem* 1996, *39*, 1651-1663; Clark, D. E.; Frenkel, D.; Levy, S. A.; Li, J.; Murray, C. W. et al., *J Comput Aided Mol Des* 1995, *9*, 13-32; Ludi *Ludi*; Accelrys Inc.: San Diego. In the case of *de novo* design, consideration of a ligand's conformations and the ionic state of its functional groups are not critical problems, because the *de novo* design programs generate functional groups in suitable forms and suitable conformations to interact with the protein surface. A further advantage of the *de novo* design programs is that they can generate ligands that are comprised of novel skeletons. However, such programs may suggest ligands that are difficult to build synthetically or that are unstable, and thus it is necessary for the chemist to evaluate candidate compounds for their synthetic accessibility, and thereby to guide the *de novo* design process. Also, for compounds having too many rotatable bonds, these programs may create structures which when redocked to the recognition site, fail to show appropriate binding. Accordingly, these programs are best combined with a chemist's own knowledge and creativity, thereby leading to a more rational drug design approach. Novel structures can also be generated solely through the chemist's visual inspection of the binding site coupled with a structural knowledge of

existing ligands or the structure of ligands discovered through the 3D database search. The modeling programs, such as Autodock, DOCK, FlexX, or GOLD, are then used to dock these newly conceived ligands to the binding site, and structural modifications are made *in silico* in order to improve their fit. Goodsell, D. S.; Olson, A. J., *Proteins* **1990**, *8*, 195-202; Morris, G. M.; Goodsell, D. S.; Halliday, R. S.; Huey, R.; Hart, W. E. et al.; *J Comput Chem* **1998**, *19*, 1639-1662; Kuntz, I. D.; Blaney, J. M.; Oatley, S. J.; Langridge, R.; Ferrin, T. E., *J Mol Biol* **1982**, *161*, 269-288; Rarey, M.; Kramer, B.; Lengauer, T.; Klebe, G., *J Mol Biol* **1996**, *261*, 470-489; Rarey, M.; Kramer, B.; Lengauer, T., *Bioinformatics* **1999**, *15*, 243-250; Jones, G.; Willett, P.; Glen, R. C.; *J Mol Biol* **1995**, *245*, 43-53; Jones, G.; Willett, P.; Glen, R. C.; Leach, A. R.; Taylor, R., *J Mol Biol* **1997**, *267*, 727-748.

We refer to this approach as *de novo*/rational drug design. Estimation of how well the ligands are docked in the binding site can be performed by variety of single scoring methods, e.g., FlexX, PMF, GOLD, Chemscore or DOCK, although, it has been reported that a consensus of several independent functions outperforms a single scoring function. FlexX *FlexX*; 6.8 ed.; Tripos Inc.: St. Louis; Muegge, I.; Martin, Y. C., *J Med Chem* **1999**, *42*, 791-804; Jones, G.; Willett, P.; Glen, R. C., *J Mol Biol* **1995**, *245*, 43-53; Jones, G.; Willett, P.; Glen, R. C.; Leach, A. R.; Taylor, R., *J Mol Biol* **1997**, *267*, 727-748; Eldridge, M. D.; Murray, C. W.; Auton, T. R.; Paolini, G. V.; Mee, R. P., *J Comput Aided Mol Des* **1997**, *11*, 425-445; Kuntz, I. D.; Blaney, J. M.; Oatley, S. J.; Langridge, R.; Ferrin, T. E., *J Mol Biol* **1982**, *161*, 269-288; Bissantz, C.; Folkers, G.; Rognan, D., *J Med Chem* **2000**, *43*, 4759-4767; Clark, R. D.; Strizhev, A.; Leonard, J. M.; Blake, J. F.; Matthew, J. B., *J Mol Graph Model* **2002**, *20*, 281-295. In order to prioritize ligands for synthesis or further improvement, they should be ranked using either single scoring function values or scores produced by more sophisticated ranking procedures, such as "rank-by-rank", "rank-by-number" or "rank-by-vote". Wang, R.; Wang, S., *J Chem Inf Comput Sci* **2001**, *41*, 1422-1426.

Among other structure-based design tools available to medicinal chemists, the virtual combinatorial chemistry approach is probably one of the most powerful methods for exploring chemical space. Unfortunately, despite the increasing throughput of parallel synthesis and screening technologies, the number of compounds that can be synthesized is far too large to permit their *in vitro* screening. A common solution to this problem is to "virtualize" the combinatorial libraries and to apply appropriate selection procedures to

limit compounds for chemical synthesis and biological testing. In general, the virtual combinatorial library approach consists of two major phases; during the first phase, virtual reactant-based or product-based virtual combinatorial libraries are generated using programs such as Legion, Analog Builder, or CombiLibMaker. Legion *Legion*; 6.8 ed.; Tripos Inc.: St. Louis; Builder, A. *Analog Builder*; Accelrys Inc.: San Diego; CombiLibMaker *CombiLibMaker*; 6.8 ed.; Tripos Inc.: St. Louis. During the second phase, the resulting databases of combinatorially generated chemical structures are subjected to docking and scoring using the methods of *in silico* screening developed for the docking and scoring of 3D databases and ligands designed using *de novo* methods. It should be noted that these methods can be used for both lead optimization and generation of new leads for further drug design, since the combinatorial library generators can create libraries varying either the sidechains or the core structure of a potential ligand.

The increased computational ability of modern computers and successes in parallel computational methods allows one to dock and score thousands of compounds in hours, leading to the gradual replacement of *de novo* methods, such as Ludi and LeapFrog, with combinatorial or *de novo* combinatorial methods of drug design. A number of attempts have been made to combine the power of *de novo* and virtual combinatorial methods of drug design. For instance, the combinatorial small molecule algorithm, CombiSMOG, grows a ligand from a small starting fragment in a stepwise manner by replacing all possible variation groups in the growing fragment with a number of predefined fragments while simultaneously evaluating the attached group for favorable or unfavorable interactions. DeWitte, R. S.; Shakhnovich, E., *Abstr Pap Am Chem S* **1997**, *214*, 6-Comp; Grzybowski, B. A.; Ishchenko, A. V.; Kim, C. Y.; Topalov, G.; Chapman, R. et al., *P Natl Acad Sci USA* **2002**, *99*, 1270-1273. The best candidates and a small number of "poor" ligands enter the next iteration. As in all *de novo* methods, evaluation of the resulting ligands by a chemist is essential to ensure their synthetic feasibility and chemical stability.

Another method that allows rapid virtual combinatorial screening and incorporates some elements of *de novo* design is CombiFlexX. CombiFlexX *CombiFlexX*; 6.8 ed.; Tripos Inc.: St. Louis. In this approach, the core molecule is positioned and held fixed in the binding site while each newly added substituent is independently attached, flexibly docked using FlexX, and scored using CScore. FlexX *FlexX*; 6.8 ed.; Tripos Inc.: St. Louis; CScore *CScore*; 6.8 ed.; Tripos Inc.: St. Louis. The method is based on the assumption that

the score of a whole molecule can be represented as a sum of the scores of the core structure and the added substituents. As a result, docking the whole combinatorial library using CombiFlexX is orders of magnitude faster than docking the same set of ligands using common docking programs such as Dock and FlexX. Moreover, in this method, synthetic feasibility is easily controlled during the design phase of the combinatorial library.

In preliminary molecular modeling studies, the 3D structure of PPARγ (PDB : 1K74) in the Protein Data Bank was used. The SiteID module in Sybyl was then applied to map the space in the binding cavity that is available to a ligand. The surface identified by SiteID was mapped by electrostatic, lipophilic, and H-bonding potentials using the MOLCAD module in Sybyl. The resulting models were then used for building the 3D query and for the *de novo*/rational design of new ligands. To simplify further descriptions of ligand-binding, the binding site of PPARγ was separated into six hypothetical binding pockets that are marked L1, U1, M, U2, L2, and U3.

Optimization of docking, scoring, and ranking procedures for PPAR ligands

To verify the docking accuracy of the FlexX module in Sybyl, five known ligands (see Figure 3) shown in Table 1 were docked into PPARγ using the FlexX module (Sybyl) and scored using the CScore module (Sybyl). The structures of the resulting docked compounds were compared to the corresponding x-ray structures, if available, of these ligands co-crystallized in the LBD of PPARγ. In general, FlexX itself and the scoring functions implemented in CScore (FlexX, DOCK, PMF, Chemscore, Gold) performed well and were able to reproduce the position of the ligand within the binding site of PPARγ. Of critical importance is the determination of the scoring function that should be used for ranking potential hits. For our work, a scoring method similar to that used by Rognan et al. was chosen. Ligand docking is performed using FlexX and the resulting best 30 poses selected by FlexX are stored for further analysis. Bissantz, C.; Folkers, G.; Rognan, D., *J Med Chem* **2000**, *43*, 4759-4767. Since, the consensus of several independent functions generally outperforms a single scoring function, FlexX, PMF, Gold, Chemscore and DOCK scores with a consensus score of 3 were used to select the best pose for each ligand and to rank the ligands in hit lists. Bissantz, C.; Folkers, G.; Rognan, D.; *J Med Chem* **2000**, *43*, 4759-4767; Clark, R. D.; Strizhev, A.; Leonard, J. M.; Blake, J. F.; Matthew, J. B.; *J Mol Graph Model* **2002**, *20*, 281-295.

Table 1. *In silico* and *in vitro* screening results of known PPARγ agonists. pEC_{50} of *in vitro* activation of PPARγ, scores, and ranks used to determine the best scoring model for scoring new PPARγ agonists.

Compound	pEC_{50}	*in vitro* rank	*in silico* rank					Score				
			DOCK	PMF	GOLD	Chem -score	FlexX	DOCK	PMF	GOLD	Chem -score	FlexX
Ligand **3q**	6.77	5	4	4	3	4	4/5	-170	-83	-252	-47	-21
Rosiglita-zone	6.80	4	5	5	5	5	4/5	-147	-53	-223	-37	-21
Ligand **3p**	7.96	3	3	3	4	3	3	-172	-85	-229	-48	-22
Gi262570	8.94	2	1	2	2	1	1	-238	-115	-312	-65	-32
GW409544	9.55	1	2	1	1	2	2	-226	-120	-335	-56	-29
	Correlation coefficients between scores and pEC_{50}s							-.906	-.906	-.873	-.815	-.880

All scoring functions showed relatively high correlation coefficients between scores and pEC_{50}. Although all functions made errors in their relative ranking of ligands, the PMF function performed better than the other functions, as it made only one rather insignificant error, switching the ranking of the moderately active ligand, rosiglitazone, with that of **3q**. Based on these findings, the PMF scoring function shows the best docking and scoring accuracy and was used in further studies. All functions successfully identified Gi262570 and GW409544 as the two best ligands, whereas, **3p**, **3q** and rosiglitazone were identified as the least active, suggesting that all functions are able to choose between active and moderately active ligands. Detailed results of *in silico* screening using the PMF score and a consensus of three or more scoring functions are shown in Table 2. The RMS difference between the docked and x-ray poses are within the absolute value of the error of the X-ray experiments.

Table 2. RMS deviation (non hydrogen atoms) of PPARγ agonists docked by FlexX (best PMF score, consensus of 3 or more) from the X-ray pose and identification of pockets occupied by the ligands.

Structure	Pockets occupied	Comments
GW409544	L1, U1, M, L2, U2	PDB 1K74, RMS = 2.23 Å, x-ray resolution 2.3 Å
Rosiglitazone	L1, U1, M, L2, U2	PDB 2PRG, RMS = 1.85 Å, x-ray resolution 2.3 Å
Gi262570	L1, U1, M, L2, U2	PDB 1FM6, RMS = 1.45 Å, x-ray resolution 2.3 Å

3D Search for compounds containing COOH and two 5- or 6-membered aromatic or heteroaromatic rings

As discussed, potent PPAR agonists bind to the L1, U1, M, and L2 regions or to the U1, M, and L2 regions and contain a polar group, such as a carboxyl or thiazolidinedione group, that is able to form strong interactions with the polar region of U1. Based on this binding mode, an approximate pharmacophore model was constructed, comprising: 1) a polar group that is able to bind to the polar binding site of U1; and 2) at least two rigid groups, such as an aromatic ring, in order to provide proper orientation of the polar group in the binding site while reducing entropy. The latter requirement is important as it has a marked effect on the binding energy. Visual analysis of the binding site and sample docking experiments showed that ligands with a carboxyl group in U1 and aryl groups in regions L1 and M fit well, and that the positions of the sample ligands resemble the positions of the highly active tyrosine-based compounds.

To perform a 3D search of the NCI database, the 3D UNITY database module in Sybyl was used. In the first stage, the NCI 3D-database of 127K "open" compounds was searched using the query shown in Figure 4A. As an additional restriction for this search, a slightly modified version of Lipinsky's "rule of 5" was applied; specifically, a compound was considered to be a hit only if its molecular weight was more than 199 and less than 650. A total of 19,356 hits were obtained. Next, distance restrictions were introduced (Figure 4B) and the resulting hit list was searched again. At this stage, only one conformation for each compound stored in the 3D NCI database was used. This search resulted in a total of 7,895 hits. The resulting hit list was further subjected to a flexible 3D search using the pharmacophore model shown in Figure 4C. During this procedure up to 10 conformations were generated for each of 7,895 compounds obtained in the previous step. A total of 704

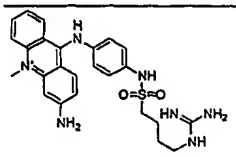
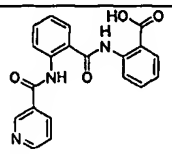
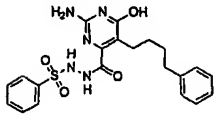
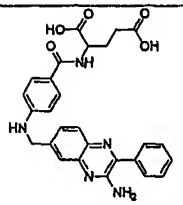
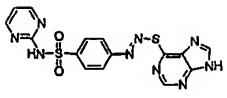
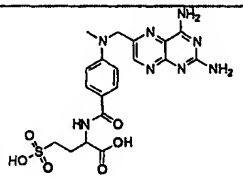
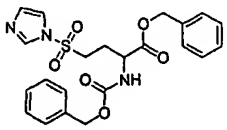
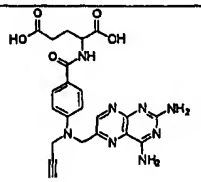
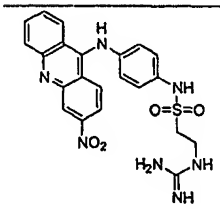
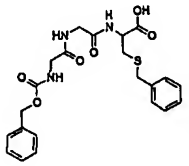
hits were obtained after this step. The resulting 704 ligands were docked into PPARγ and scored as described above.

3D Search for compounds containing an SO_2N group and two 5- or 6-membered aromatic or heteroaromatic rings

Among the hits found from the previous search, several ligands containing a sulfonamide group preferred to bind to the polar binding pocket using this group, rather than an attached carboxyl group. In general, compounds bearing a sulfonamide group show high FlexX and PMF scores suggesting this group as a possible candidate for the 3D database search. A new query containing a sulfonamide group in place of the carboxyl group was generated (Figure 5). A 2D search using the query shown in Figure 5A afforded 4,807 compounds that were subjected to a 3D search using the query shown in Figure 5B. A total of 10 conformations were searched for each of the 4,807 compounds. This step produced 953 compounds that were docked to PPARγ and scored as described above. The best 39 ligands were considered for further analysis.

The compounds obtained from the two 3D searches were combined, and ligands containing chemical groups potentially unstable to the assay conditions were removed. The top ten ligands are shown in Table 3. Most of the ligands identified by this 3D database search showed PMF scores comparable to or better than those of the known ligands based on a comparison of the data in Table 1 with the data in Table 3.

Table 3. Top 10 potential PPARγ agonists identified by 3D database search and *in silico* screening in NCI database.

Structure	PMF score	Pockets occupied	NCI code	Structure	PMF score	Pockets occupied	NCI code
	-122	L1, U1, M, U2	172774		-136	U1, L1, M	351092
	-119	L1, U1, M	210898		-97	U1, M, U2, U3	662795
	-119	U1, M, U2, U3	117022		-94	U1, M, U2, L2	696559
	-117	L1, U1, M, U2	270905		-94	U1, M, U2, L2	334052
	-117	L1, U1, M, U2	177366		-84	L1, U1, M, U2, U3	338489

De novo/rational design of PPAR agonists containing new scaffolds and their in silico screening results

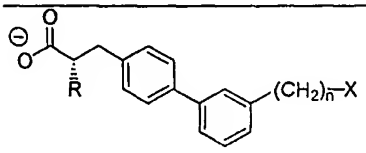
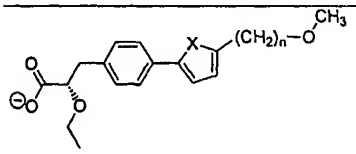
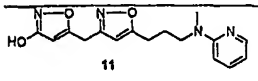
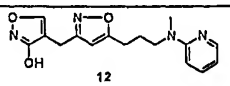
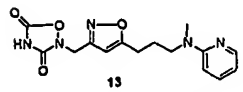
Our *de novo*/rational design efforts were based in part on the SAR available for the known ligands. The ligand-binding cavity was divided into six hypothetical regions U1, L1, M, U2, L2, and U3, and the importance of each of these was determined. The binding modes of the ligands were analyzed within each of the three PPAR isoforms.

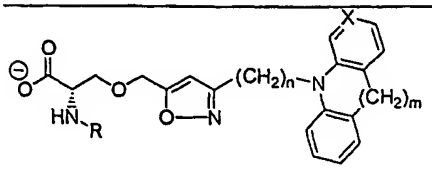
The region U1 of PPARγ is polar and is comprised of tyrosine residues Tyr,[327,473] histidine residues His,[323,449] and serine residue Ser.[289] The vast majority of PPAR agonists contain a polar carboxyl polar group that interacts with the pocket U1. The region L1 is lipophilic, and it is able to accommodate relatively large substituents such as a diphenylketone group. The bottom of the L1 region consists of three phenylalanine residues Phe[282,360,363] and is able to participate in π-π interactions with complementary groups present in the ligands. According to Cobb et al., the L1 region in PPARγ is the "potency enhancement region." Cobb, J. E.; Blanchard, S. G.; Boswell, E. G.; Brown, K. K.; Charifson, P. S. et al., *J Med Chem* 1998, *41*, 5055-5069. Therefore, the presence of functional groups in a ligand that can interact favorably with L1 is desirable. Binding to the regions L1 and U1 that are close to AF2 helix was found to be more important than binding to the regions L2, U2, and U3. For instance, ligand GW0072 occupies pockets L2, U2, and U3 and exhibits only partial agonistic properties, whereas, ligands occupying the L1, U1, M, U2, and L2 pockets or only the U1, M, U2, and L2 pockets show full agonistic effects. Willson, T. M.; Brown, P. J.; Sternbach, D. D.; Henke, B. R., *J Med Chem* 2000, *43*, 527-550. Based on this description, four new classes of potential PPAR agonists were constructed using Leapfrog (Sybyl) and our chemical knowledge.

The results for a representative set of ligands selected from the entire set of ligands for each core structure are shown in Table 4. In general, the poses of the newly designed ligands resemble the poses of the known ligands co-crystallized with PPARγ. The biaryl-, isoxazolyl-, and triheterocyclic-based ligands shown in Figure 6 were designed to bind to regions U1, M, U2, and L2 or U3, although some are also able to bind to the potency enhancement region L1 if they contain a substituent that is long enough to reach the phenylalanine residues Phe[282,360,363]. In general, the interaction mode of such ligands with L1 resembles that of the known tyrosine-based ligands where a lipophilic substituent connected to the N-atom of tyrosine occupies region L1. It was hypothesized that this region could be reached by sidechains connected to structural elements other than the N-atom of tyrosine. Based on this idea, 2,4-dihydroxyphenylalkanoic acid, 3-(2,4-dihydroxyphenyl)alanine, and 6-hydroxyindole-3-acetic acid were proposed as potential core structures. The data provided in Table 4 show that our hypothesis may be correct, as some of these ligands are able to bind to the L1 pocket, and on the average, those ligands binding to L1 have higher PMF scores than those without substituents in L1. The top 5-10

ligands for each core structure identified by the *de novo*/rational design approach showed PMF scores comparable to those of the known ligands (Table 1), suggesting that these cores have the appropriate structural organization required for PPAR binding.

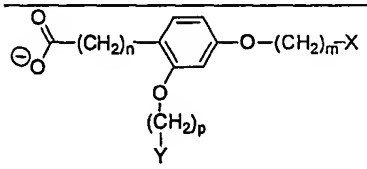
Table 4. Results of the *in silico* screening of the best ligands designed using *de novo*/rational drug design approach.

Cmpd	Substituents	PMF score	Pockets occupied
			
Biaryl-based ligands			
1	n = 4, X = OCH_3, Y = H, R = OCH_2CH_3	-72	U1, M, U2, U3
2	n = 4, X = OCH_3, Y = H, R = $NHCOCH_3$	-74	U1, M, U2, U3
3	n = 3, X = OCH3, Y = H, R = OEt	-79	U1, M, U2, U3
4	n = 2, X = CO_2CH_3, Y = H, R = OEt	-86	U1, M, U2, U3
5	n = 2, X = CO_2CH_3, Y = H, R = $NHSO_2CH_3$	-83	U1, M, U2, U3
			
Biaryl-based ligands			
6	n = 4, X = S	-78	U1, M, U2, L2
7	n = 4, X = N	-70	U1, M, U2, U3
8	n = 2, X = S	-76	U1, M, U2, U3
9	n = 2, X = N	-80	U1, M, U2, U3
10	n = 1, X = S	-76	U1, M, U2, U3
 11			
 12			
 13			
Triheterocyclic ligands			
11		-67	L1, U1, M
12		-62	U1, M, U2
13		-82	L1, U1, M



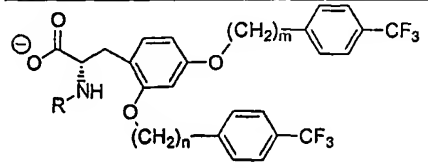
Isoxazolyl-serine/cysteine-based ligands

14	n = 5, m = 0, X = CH, R = CH_3	-82	U1, M, U2, U3
15	n = 5, m = 0, X = CH, R = SO_2CH_3	-98	L1, U1, M, U2, U3
16	n = 3, m = 0, X = N, R = CH_3	-89	U1, M, U2
17	n = 3, m = 0, X = N, R = SO_2CH_3	-91	L1, U1, M, U2
18	n = 3, m = 0, X = N, R = SO_2Ph	-106	L1, U1, M, U2
19	n = 3, m = 0, X = N, R = $COCH_3$	-103	U1, M, U2, L2



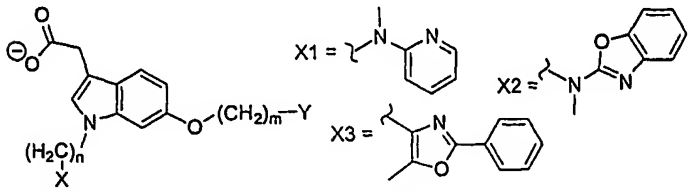
2,4-Dihydroxyphenylalkanoic acid-based ligands

20	n = 2, m = 0, p = 3, X = Ph, Y = Ph	-104	U1, M, U2, L2
21	n = 2, m = 0, p = 2, X = *p*-CF_3-Ph, Y = Ph	-105	L1, U1, M, U2
22	n = 2, m = 0, p = 2, X = Ph, Y = Ph	-104	L1, U1, M, U2
23	n = 2, m = 0, p = 2, X = *p*-$PhCH_2CH_2OCH_3$, Y = *p*-$PhCF_3$	-103	L1, U1, M, U2, U3
24	n = 2, m = 0, p = 2, X = *p*-$PhCH_2CH_2OCH_3$, Y = *o*-$PhCF_3$	-106	L1, U1, M, U2, U3
25	n = 2, m = 3, p = 2, X = X1, Y = Ph	-103	L1, U1, M, U2, U3



3-(2,4-Dihydroxyphenyl)alanine-based ligands

26	n = 4, m = 4, R = CH_3	-53	L1, U1, M, U2, U3
27	n = 3, m = 3, R = CH_3	-75	L1, U1, M, U2, U3
28	n = 3, m = 3, R = SO_2CH_3	-111	L1, U1, M, U2, L2
29	n = 2, m = 2, R = CH_3	-43	U1, M, U2, U3



6-Hydroxyindole-3-acetic acid-based ligands

30	n = 3, m = 2, X = Ph, Y = Ph	-115	L1, U1, M, U2, L2
31	n = 3, m = 2, X = Ph, Y = X1	-122	L1, U1, M, U2, L2
32	n = 3, m = 2, X = Ph, Y = X2	-110	L1, U1, M, U2, L2
33	n = 3, m = 2, X = Ph, Y = X3	-119	L1, U1, M, U2, L2
34	n = 3, m = 2, X = Ph, Y = 2-naphtyl	-101	L1, U1, M, U2, L2

Design and in silico screening of a combinatorial library based on the 2,4-dihydroxyphenylalkanoic acid core

A combinatorial library based on the 2,4-dihydroxyphenylalkanoic acid core and the modifications shown in Figure 7 was generated using the Legion module in Sybyl. A total of 660 ligands was generated. The resulting Sybyl database was translated to the UNITY database, and 3D structures were generated using Concord. Next, the library was docked to PPARγ, scored and ranked using the procedure described in Section C-1. The top ten ligands generated by this method are shown in Table 5. Despite the fact this combinatorial library is limited in number, this method was able to produce ligands exhibiting PMF scores better than those of the original 6-hydroxyindole-3-acetic acid-based ligands designed using the *de novo*/rational approach (Table 4) and the best tyrosine-based ligands Gi262570 (-115) and GW409544 (-120) (Table 1).

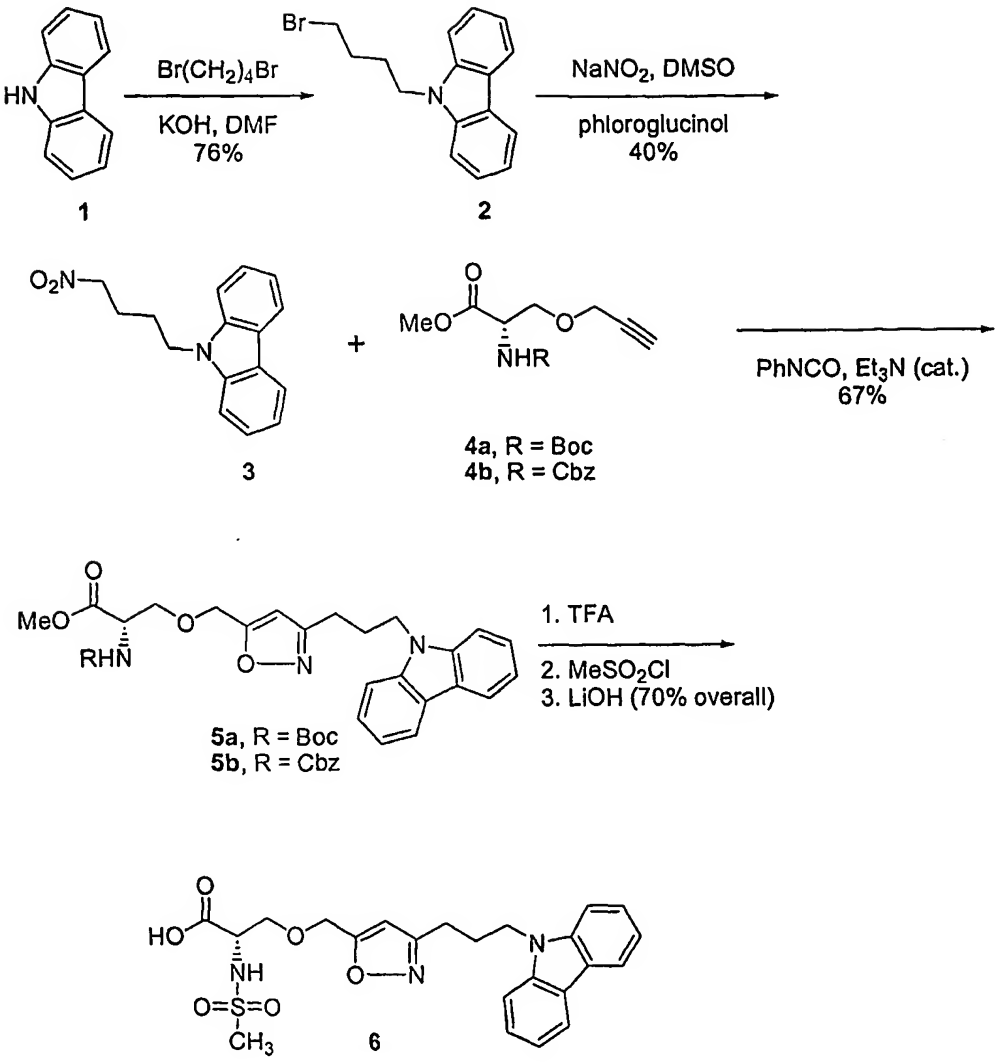
Table 5. Top 10 2,4-dihydroxyphenylalkanoic acid-based PPARγ agonists identified by the combinatorial library approach.

Structure	PMF score	Pockets occupied	Structure	PMF score	Pockets occupied
n = 5, m = 3, X3 = *o*-$CONH_2$	-136	L1, U1, M, U2, U3	n = 4, m = 2, X3 = *m*-OEt	-123	L1, U1, M, U2, L2
n = 4, m = 3, X3 = *o*-$CONH_2$	-126	L1, U1, M, U2, L2	n = 4, m = 3, X3 = *m*-OEt	-123	L1, U1, M, U2, L2
n = 5, m = 2, X3 = *o*-$CONH_2$	-125	L1, U1, M, U2, L2	n = 1, m = 3, X3 = *m*-$CONH_2$	-122	L1, U1, M, U2, L2
n = 3, m = 2, X3 = *o*-NH_2	-124	L1, U1, M, U2, L2	n = 4, m = 2, X3 = *o*-$CONH_2$	-122	L1, U1, M, U2, L2
n = 5, m = 4, X3 = *o*-$CONH_2$	-124	L1, U1, M, U2, L2	n = 1, m = 2, X3 = *m*-$CONH_2$	-121	L1, U1, M, U2, L2

Chemistry

Synthetic work has been carried out on a class of rationally designed ligands. The method of synthesis for this isoxazolyl bearing serine analog is shown in Scheme 1. As disclosed in the Exemplification section, the present approach has been used to produce a focused library of structures bearing diverse N-substituents and terminal heterocyclic groups.

Scheme 1



Preliminary biological screening

The first 40 compounds found during the database search were requested from NCI/NIH Developmental Therapeutics Program. In fact, of the 40 compounds requested, 17 compounds were available and were screened using the procedure described herein. One of 17 compounds identified in the 3D database search exhibited PPARγ activity that was approximately 25% of the activity of GW7845. The same procedure was used to test test the isoxazolyl-based compounds described in Example 21 synthesized, in part, as in Scheme 1. The initial series of isoxazolyl-serine/cysteine-based compounds, ZW40 to ZW-

50, were screened for PPAR agonist activity at 5 μM concentration. ZW-41 (Figure 11) and ZW-53 and ZW-55 (Figure 12) activity equal to or greater than the PPARα standard, WY14643. The same series of ligands ZW-51-ZW-55 did not exhibit significant PPARγ agonist activity at 5 μM concentration (Figure 13 and Figure 14). These data identify the isoxazolyl-serine/cysteine-based series of compounds as a new class of PPARα agonists.

Summary of the preliminary results

1. The results of virtual screening are consistent with the *in vitro* results for known ligands. The *in silico* experiments are able to reproduce the position of ligands within the binding cavity (docking accuracy). The virtual screening ranks ligands correctly and the PMF scores of known ligands correlate well with their pEC_{50} (scoring accuracy). Thus, the proposed procedure of virtual screening is a reliable predictor of *in vitro* activity.

2. The 3D database search identified SO_2N as a favorable group for interaction with the polar binding site U1. The 3D search method will be expanded to identify other functional groups and scaffolds for use in PPARγ drug design.

3. All ligands with a high PMF score occupy any combination of three or more hypothetical pockets U1, L1, M, U2, L2, and U3 with the restriction that the U1 and M pockets must always be occupied. L1 is a region for potency enhancement because ligands that are able to occupy L1 are generally more active than related ligands that fail to occupy L1. It is possible to reach the L1 pocket by appropriately positioning on the PPAR scaffold a sidechain comprising a flexible linker containing a terminal aryl group. The PMF score of such ligands is comparable or higher than the PMF score of known ligands that are able to occupy L1. This observation leads to a new set of potential scaffolds in the design of active compounds.

4. *De novo*/rational design methods are able to produce new PPAR scaffolds.

5. Application of the virtual combinatorial library approach to PPAR ligands has been shown to be able to improve upon ligands designed using *de novo*/rational design methods.

Strategy for the PPAR Drug Discovery

A PPAR drug discovery strategy of the present invention to discover PPAR ligands comprises a 3D database search, *de novo*/rational drug design, and virtual combinatorial

methods (collectively referred to as phase one) (Figure 9). The best ligands obtained from phase one entered phases 2, 3, and 4; that is, they were screened *in silico* (phase 2), and the best candidates were synthesized (phase 3) and tested *in vitro* for PPAR activity and selectivity (phase 4). In phase five, the results of the PPAR isoform-selective biological assays will be used to further optimize ligand activity and selectivity using the methods developed in phase 1. For ligands showing an $EC_{50} < 1$ μM, their antiproliferative and apoptotic effects will be examined in human cancer cell lines (phase 6). It is possible that the newly designed ligands may fail to penetrate the cell membrane. In this case, the ligands will be further modified, eg. deletion of heteroatoms, pro-drug modifications, etc. to improve their cell permeability.

In silico screening of available chemical databases

During our preliminary research, we used a simplified pharmacophore model for virtual structure-based screening of the NCI database in order to speed up the search procedure. We then conducted a broader search using a more descriptive pharmacophore model having fewer restrictions as to the presence of certain functional groups. The binding site surface determined with the SiteID software (SYBYL) was used to build a 3D query for flexible searching of the 3D NCI and MDL/ACD databases. The 3D search was performed using the UNITY module in SYBYL. In addition to imposing volume restrictions, the 3D query included such features as hydrogen bond and hydrophobic sites. The compounds obtained at this stage were docked to PPAR α, δ, and γ and scored. The 1000 best compounds, i.e., having either the highest activity or selectivity for PPARγ, were then minimized in the binding site and rescored. They were also visually examined to ensure good shape complementarity and interaction mode. The best compounds were then tested in the PPAR assays.

The scoring procedures for the PPARα and δ isoforms were optimized using the same approach as presented earlier. This approach was important for gaining a measure of PPAR selectivity of our ligand hits. The best ranking model was modified continually to achieve the best "hit rate". Different ranking models ("rank-by-rank", "rank-by-number", and "rank-by-vote") were examined, and the best scoring method was used.

De Novo/Rational Drug Design

De novo design and lead optimization was aided using the Ludi program implemented in InsightII. Ludi *Ludi*; Accelrys Inc.: San Diego. Basically, molecules were fitted to the ligand-binding domain of PPARα, δ, and γ, and functional groups were added or deleted so as to enhance ligand-protein interactions through increasing hydrophobic interactions, H-bond contacts, etc. The newly modeled compounds were then screened *in silico* as described herein; and the best candidates were synthesized and studied using the PPAR assays. Depending upon the biological results, the process would be repeated if required, through another stage of modeling and assay in order to optimize compound potency and selectivity. Therefore, this process of modeling, synthesis, and biological assay may be performed in an iterative fashion.

Design and in silico screening of virtual combinatorial libraries

A candidate core molecule was subjected to retrosynthetic analysis and visual inspection after docking into the binding site of PPARγ in order to identify major components of the ligand molecule (Figure 10), such as a "core" (also referred to as "backbone" or "scaffold") and "sidechains" (also referred to as "variations"). The resulting cores and sidechains were used to generate virtual combinatorial libraries using the Legion module in Sybyl. To achieve meaningful molecular diversity, not only was the length of the linkers in the sidechains modified, but also variation points on the sidechains and cores were modified (Figure 11) using functional groups from different Hansch clusters (Table 6).

Table 6. M embers of Hansch clusters that will be used for generation of combinatorial libraries.

Cluster number	
1	Me, Et, $CH=CH_2$, CH_2CH_2COOH, CH_2OH
2	CH=CHCOOH
3a	CN, NO_2, COOH, COMe
3b	C≡CH, CH_2Cl, Cl, CH=NOH, CH_2CN, OCOMe, COOMe, SCN, COOEt
4a	$CONH_2$, CONHMe, SO_2NH_2, SO_2Me
4b	NHCHO, NHCOMe, $NHCONH_2$, $NHCSNH_2$, $NHSO_2Me$
5	F, OMe, NH_2, $NHNH_2$, OH, NHMe, NHEt, NMe_2, OEt
6	Br, CF_3, I
7	CH_2Br, $NHCO_2Et$
8	-
9	Pr, *i*-Pr, NHBu, *t*-Bu
10	-

The diversity of physicochemical and structural properties of the sidechains and cores resulting from this approach allowed us to determine favorable physicochemical and structural characteristics of core structures and sidechains early in the lead modification process. Potential monovalent, bivalent, and trivalent variation sites (as defined in Legion) in the core groups and sidechains were identified and used for building the virtual libraries. The resulting combinatorial libraries containing 2D structures were converted to combinatorial libraries with 3D structures using the UNITY and CONCORD modules in Sybyl. Next, the combinatorial libraries were docked, scored, and ranked as described herein.

To prioritize ligands for synthesis and to find new cores, a methodology incorporating the power of *de novo* drug design and the flexibility of the combinatorial approach was employed. *In silico* lead optimization was performed during the initial design of new scaffolds for the PPAR agonists as well as after a new lead compound had been identified from the PPAR assays. The focused combinatorial library approach was used for lead optimization by following pathway A-B-C of Figure 12. An iterative scheme of

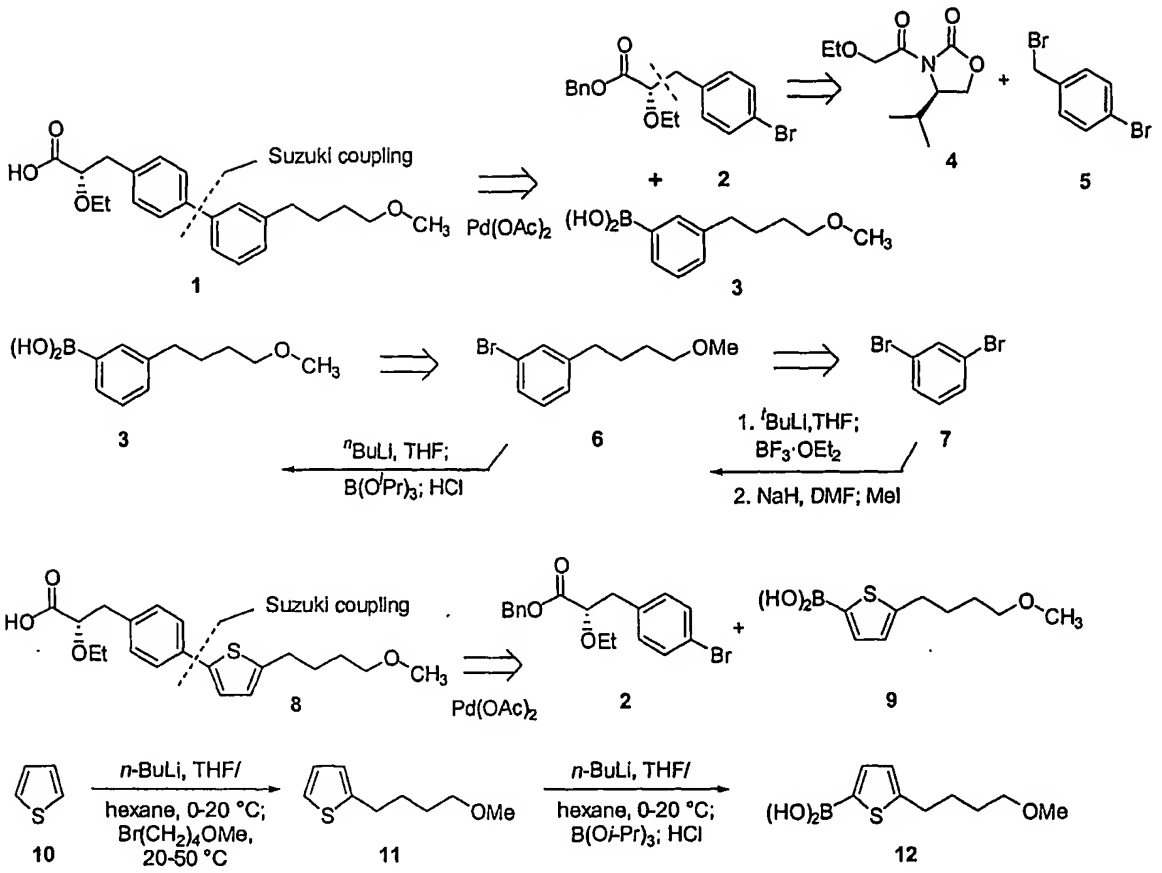
optimization of substituents and scaffolds based on alternate changes in substituents and scaffolds will be used in the design of new leads (Figure 12, pathway A-B-D-E). The resulting virtual library was docked into the binding sites of the PPARs and scored. The best ligands were selected either for further optimization of the substituents or for the generation of new core structures. See Figure 12.

Chemistry

Synthesis of Ligands Containing a Biaryl Core

A biphenyl compound **1** emerged as another interesting ligand from the *de novo* design approach. This ligand shows a PMF score of –86, and occupies regions U1, M, U2 and U3 of PPARγ. This compound and its analogs can readily be prepared from the Suzuki coupling of the boronic acid moiety **3** with the corresponding bromophenylpropionate **2** (Scheme 2). Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L., *J Am Chem Soc* **1999**, *121*, 9550-9561; Littke, A. F.; Dai, C. Y.; Fu, G. C., *J Am Chem Soc* **2000**, *122*, 4020-4028.

Scheme 2



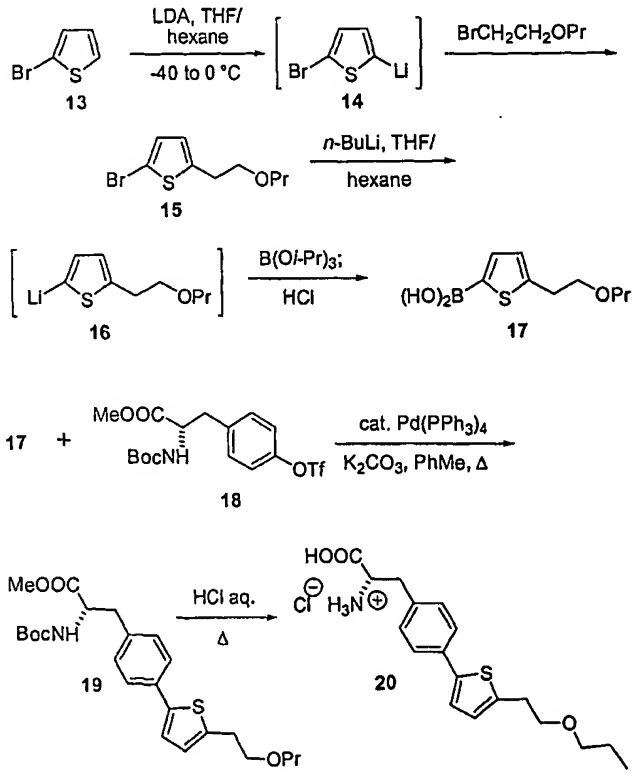
The latter compound would be assembled in optically pure form using the diastereoselective alkylation of a glycolate oxazolidinone **4**. Crimmins, M. T.; Emmitte, K. A.; Katz, J. D., *Org Lett* **2000**, *2*, 2165-2167. The required boronic acid **3** can be assembled from *m*-dibromobenzene (**7**) by halogen-metal exchange, reaction with THF with ring opening, O-methylation, and a second halogen-metal exchange followed by reaction with triisopropyl borate. Larsen, R. D.; King, A. O.; Chen, C. Y.; Corley, E. G.; Foster, B. S. et al., *J Org Chem* **1994**, *59*, 6391-6394; Eis, M., Wrobel, J. E., Ganem, B., *J Am Chem Soc* **1984**, *106*, 3693-3694. The biaryl analog **8** containing a thiophene ring also exhibits a good PMF score, and as illustrated can be assembled in a similar fashion. Sequential metallation of thiophene (**10**) followed by trapping with the appropriate electrophile would provide the required boronic acid **12** as illustrated. Brandsma, L., Verkruijsse, H *Preparative Polar Organometallic Chemistry 1*; Springer: Berlin, 1987; 115-117 and 121-127.

This series of ligands will be expanded by examining the result of modifications not

only to the biphenyl moiety, but to the substituent alpha to the acidic group (substituted amino group), the length of the alkyl chain connecting the biaryl moiety to the terminal methoxy group, as well as to the terminal substituent as diagrammed in Figure 13.

An example of the synthesis of a thienylphenyl analog **20** containing a phenylalanine moiety is illustrated in Scheme 3. The metalation of 2-bromothiophene (**13**) with LDA is known, as is the Suzuki arylation of a tyrosine-derived aryl triflate **18**. Shieh, W. C.; Carlson, J. A., *J Org Chem* 1992, *57*, 379-381; Brandsma, L., Verkruijsse, H *Preparative Polar Organometallic Chemistry 1*; Springer: Berlin, 1987; 156-157.

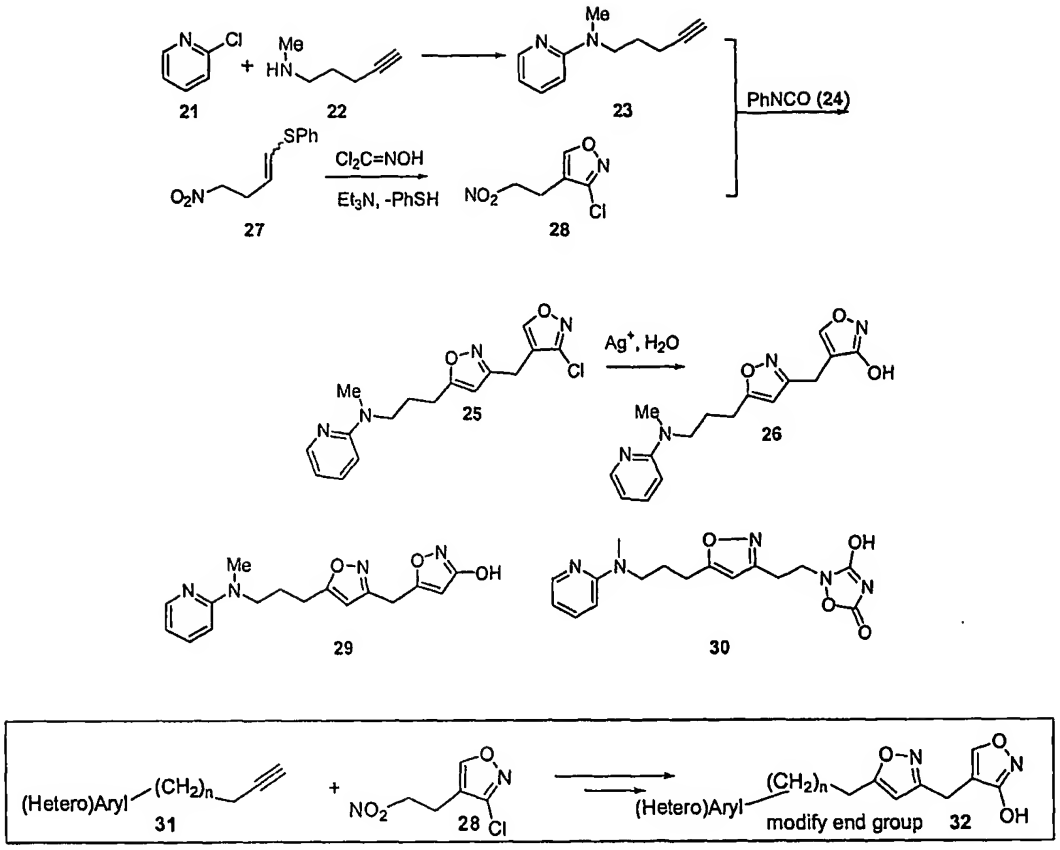
Scheme 3



Synthesis of Ligands Containing a Triheterocyclic Core

The *de novo* drug design approach coupled with principles of bioisosterism led to the selection of a bis-isoxazole **25** (compound **12** in Table 4) as a possible PPARγ ligand. In docking this ligand to PPARγ, it was found to occupy regions U1, M, and U2, and thus differs from the tyrosine-based ligands, such as GW1929, which spans the U1, M and U2 regions in addition to L1. The bis-isoxazole **26** does give a good PMF score of -62 and thus is a candidate for synthesis. The bis-oxazole ligand **26** will be constructed by use of two nitrile oxide cycloaddition reactions (Scheme 4). The first of these reactions involves cycloaddition of chloronitrile oxide to the vinyl sulphide **27** to yield isoxazole **28** after loss of thiophenol. Stevens, R. V.; Albizati, K. F. S., *Tetrahedron Letters* **1984**, *25*, 4587-4590. Next, the resulting nitro compound is reacted with phenyl isocyanate in the presence of the acetylene **23** to give chloro derivative **25**. Lastly, silver assisted hydrolysis of the chloroisoxazole **25** furnishes the required hydroxyisoxazole **26**. This approach is versatile, as any of a host **31** of aryl or heteroaryl (indole, benzofuran, carbazole, β-carboline, xanthene, etc.) bearing acetylenes can be used in the dipolar cycloaddition reaction with **28**. Thus, a small library of compounds **32** with variable end groups can be assembled by solution phase parallel synthesis for testing in the PPAR assays. The activity of a family of structurally related triheterocycles such as **29** and **30** (cmpds **11** and **13** in Table 4) will also be examined. These compounds dock to PPARγ in a slightly different way from compound **26**, occupying the L1, U1, and M pockets. Compound **29** can be prepared by a route similar to that already proposed, however, the first cycloaddition reaction would use 4-nitrobutyne as dipolarophile.

Scheme 4

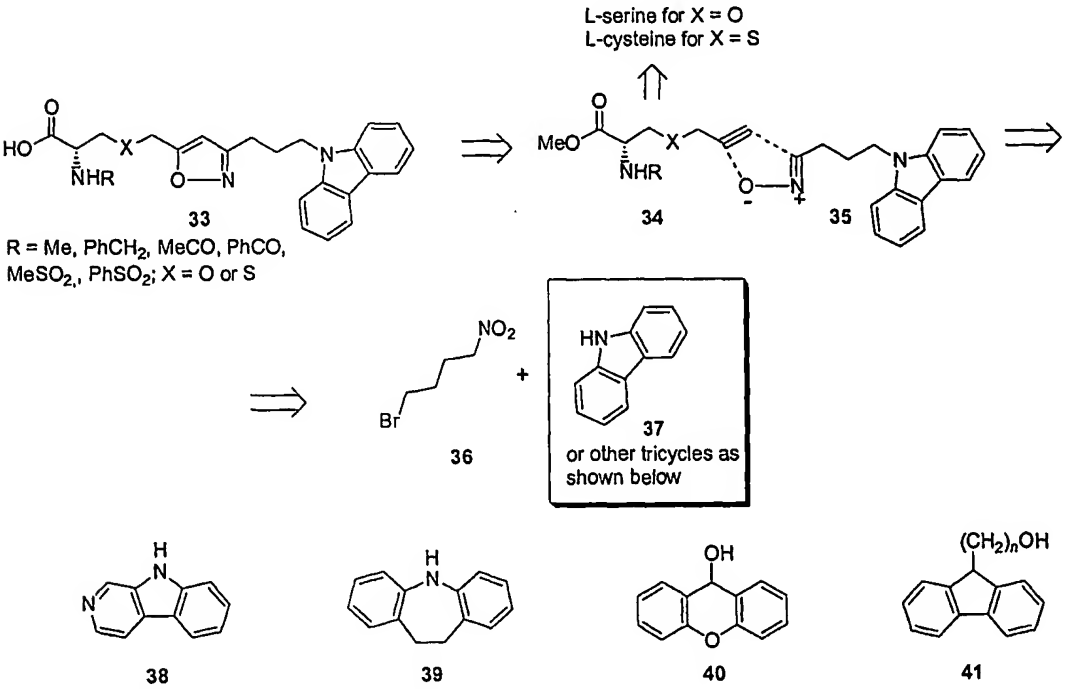


Synthesis of Ligands Containing an Isoxazolyl-Serine/Cysteine Core

Another ligand that emerged from the *de novo* design approach is the L-serine-containing structure **33**. From *in silico* screening, these ligands would occupy pockets L1, U1, M, U2, and a portion of U3 or L2. This novel disubstituted isoxazole can be readily assembled through an intermolecular nitrile oxide **35** cycloaddition reaction with the propargyl ether **34** prepared from serine methyl ester as diagrammed retrosynthetically in Scheme 5. A library of ligands **33** will be synthesized for testing in which the R group on the amine nitrogen will be varied; methyl, benzyl, acetyl, benzoyl, methylsulfonyl, and benzenesulfonyl substituted ligands will be prepared. In addition, the effect of altering the tricyclic carbazole system **37** to other heterocyclic or carbocyclic systems will be investigated. A list of possible candidate tricycles **38-41** that are commercially available is shown below.

The proposed synthesis scheme is particularly robust in that various dipolarophiles **34** can be readily combined with diverse nitro compounds **36** to provide a combinatorial array of isoxazoles **33**. From the modeling studies, the ligand bearing a β-carboline as the terminal tricycle and a benzenesulfonyl group at the amine nitrogen gave one of the highest PMF scores of −106 (cmpd **19** in Table 4). L-Cysteine can also be substituted for L-serine to provide the analogous sulfur containing series.

Scheme 5

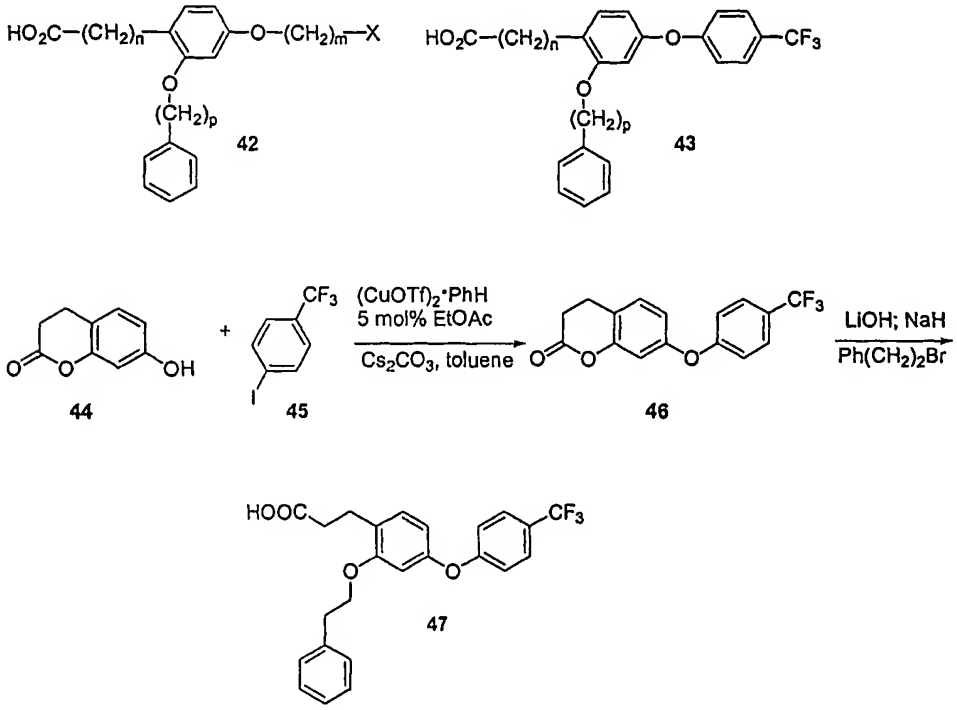


Synthesis of Ligands Containing a 2,4-Dioxyphenylalkanoic Acid Core

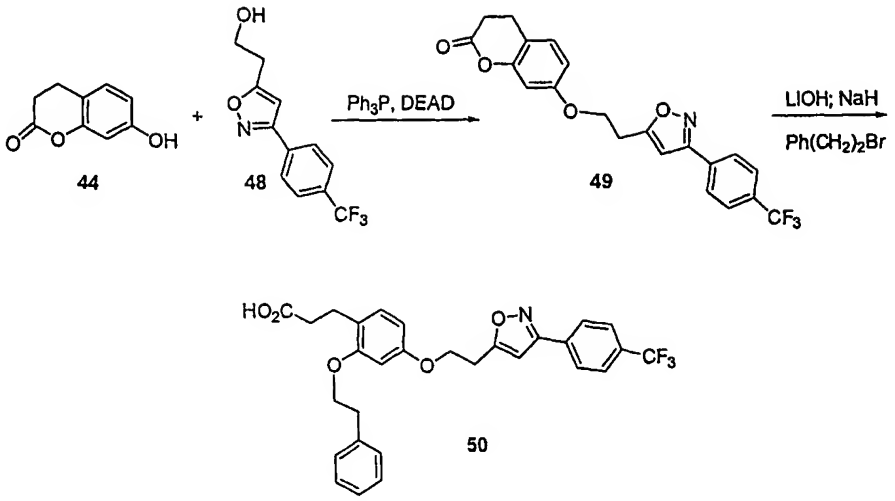
Ligands **42** and **43** containing a 2,4-dioxyphenylpropionic or 2,4-dioxyphenylacetic acid core emerged as a third category of PPAR ligands from our modeling efforts. In the case of **43** where n = 2, m = 0, p = 2, Y = Ph, and X = *p*-CF_3-Ph, the PMF score was found to be −105 (cmpd **22** in Table 4), thus suggesting that the exploration of such compounds should prove promising. The synthesis of the propionic acid derivative **47** is provided as an illustration of the possible chemistry involved in the preparation of such ligands (Scheme 6). Starting from the known dihydrocoumarin **44**, diaryl ether synthesis will be carried out using copper catalysis. Hoefnagel, A. J.; Gunnewegh, E. A.; Downing, R. S.; Vanbekkum,

H., *J Chem Soc Chem Comm* 1995, 225-226; Marcoux, J. F.; Doye, S.; Buchwald, S. L., *J Am Chem Soc* 1997, *119*, 10539-10540. Next, the lactone **46** is opened under basic conditions, and alkylation of the phenolic oxygen carried out using phenylethyl bromide as electrophile to furnish the desired acid 47. Synthesis of a related structure **50** bearing a phenylisoxazolyl moiety (PMF score = -103, cmpd **26** in Table 4) through use of a Mitsunobu coupling reaction is also shown (Scheme 7). The chemistry is straightforward and is readily amenable to the creation of a small, focused library of structures containing diverse ether groups for biological screening.

Scheme 6

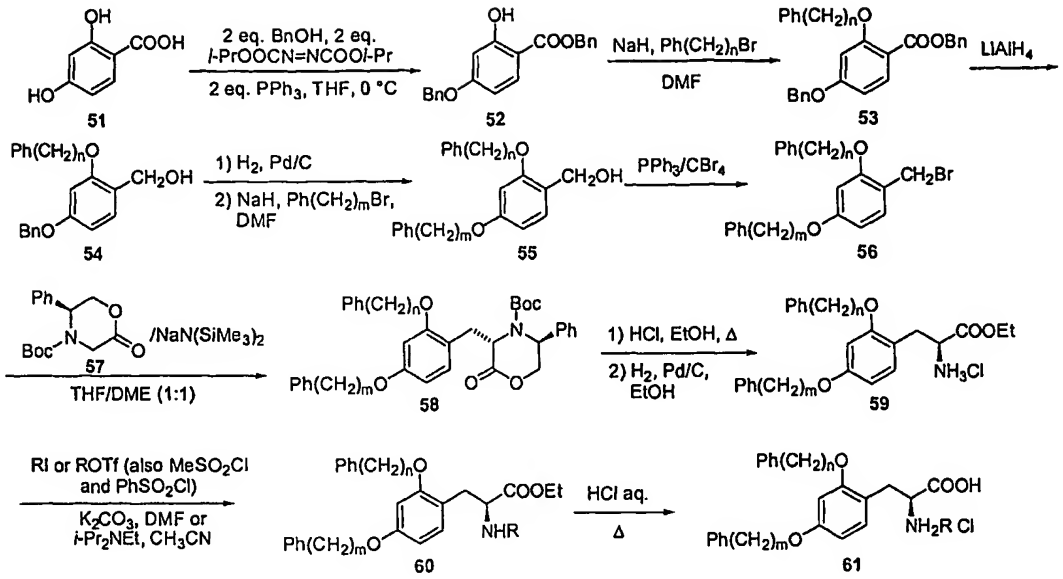


Scheme 7



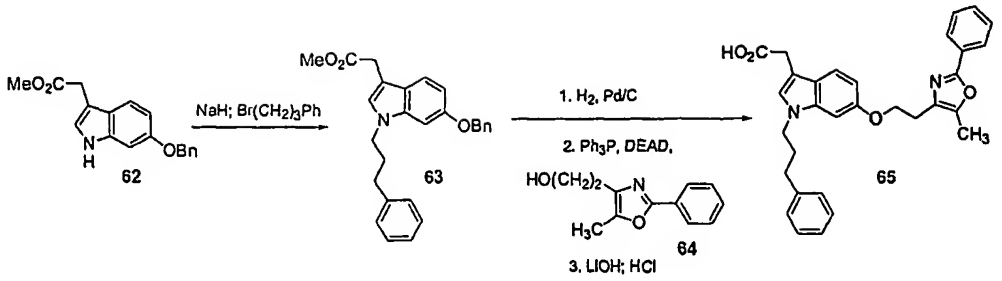
The more complex compounds containing a 3-(2,4-dioxyphenyl)alanine core gave excellent PMF scores in the modeling studies (cmpds **27-30** in Table 4). A combinatorial library of such structures can be prepared through the pathway outlined in Scheme 8. The regioselective benzylation performed in the first step has literature precedent. The enantioselective alkylation reaction used to create the α-amino acid intermediate **59** generally proceeds with high *ee* as described by Dellaria and Santarsiero. Dellaria, Jr., Joseph F.; Bernard D., *Tetrahedron Letters* **1988**, *29*, 6079-6082; Nicolaou, K. C.; Rodriguez, R. M.; Mitchell, H. J.; van Delft, F. L., *Angew Chem Int Edit* **1998**, *37*, 1874-1876.

Scheme 8

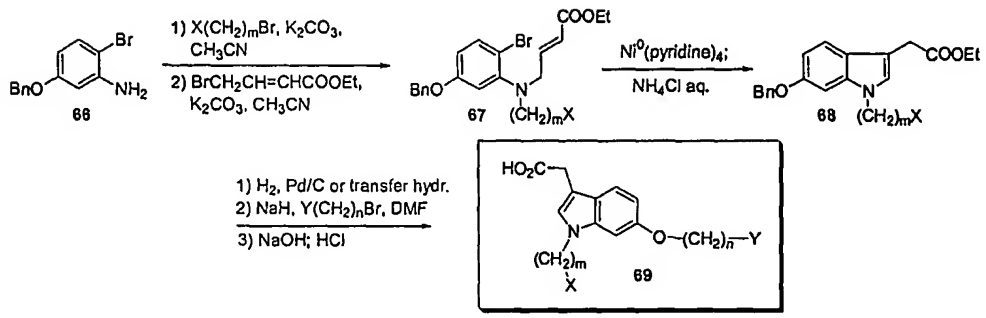


As part of this series, compounds comprised of a 6-oxyindole-3-acetic acid core will also be included. In particular, compound **65** in which the indole nitrogen bears a 3-phenylpropyl group and a phenyloxazolylethoxy substituent at the 6-position have been found to occupy the L1, U1, M, U2 and L2 pockets with a PMF score of –119. A table of some candidate indole-based ligands is provided (Table 4), and again a focused library of structures will be synthesized based upon the modeling efforts. By way of illustration, the synthesis of these ligands can be carried out starting from the known 6-benzyloxyindole acetic acid methyl ester (**62**) by N-alkylation using sodium hydride as base followed by debenyzlation. Ether formation employing the known oxazolylethanol **64** under Mitsunobu reaction conditions and ester hydrolysis completes the reaction scheme (Scheme 9). Collins, J. L.; Blanchard, S. G.; Boswell, G. E.; Charifson, P. S.; Cobb, J. E. et al., *J Med Chem* **1998**, *41*, 5037-5054. An alternative, general synthesis scheme is also shown that is based upon the use of a Heck-like reaction to assemble the indole **69** in a more direct fashion than that reported in the work of Shinada et al. Shinada, T.; Miyachi, M.; Itagaki, Y.; Naoki, H.; Yoshihara, K. et al., *Tetrahedron Letters* **1996**, *37*, 7099-7102. (Scheme 10).

Scheme 9



Scheme 10



Pharmaceutical Compositions

In another aspect, the present invention provides pharmaceutically acceptable compositions which comprise a therapeutically-effective amount of one or more of the compounds described above, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. As described in detail below, the pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; or (8) nasally.

The phrase "therapeutically-effective amount" as used herein means that amount of a compound, material, or composition comprising a compound of the present invention which is effective for producing some desired therapeutic effect in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any medical treatment.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or polyanhydrides; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

As set out above, certain embodiments of the present compounds may contain a basic functional group, such as amino or alkylamino, and are, thus, capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable acids. The term "pharmaceutically-acceptable salts" in this respect, refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These

salts can be prepared *in situ* in the administration vehicle or the dosage form manufacturing process, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed during subsequent purification. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19)

The pharmaceutically acceptable salts of the subject compounds include the conventional nontoxic salts or quaternary ammonium salts of the compounds, e.g., from non-toxic organic or inorganic acids. For example, such conventional nontoxic salts include those derived from inorganic acids such as hydrochloride, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicyclic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, and the like.

In other cases, the compounds of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable bases. The term "pharmaceutically-acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention. These salts can likewise be prepared *in situ* in the administration vehicle or the dosage form manufacturing process, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically-acceptable metal cation, with ammonia, or with a pharmaceutically-acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. (See, for example, Berge et al., *supra*)

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 1 per cent to about ninety-nine percent of active ingredient, preferably from about 5 per cent to about 70 per cent, most preferably from about 10 per cent to about 30 per cent.

In certain embodiments, a formulation of the present invention comprises an excipient selected from the group consisting of cyclodextrins, liposomes, micelle forming agents, e.g., bile acids, and polymeric carriers, e.g., polyesters and polyanhydrides; and a compound of the present invention. In certain embodiments, an aforementioned formulation renders orally bioavailable a compound of the present invention.

Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping

the product.

Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and non-ionic surfactants; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-shelled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be formulated for rapid release, e.g., freeze-dried. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically-acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms upon the subject compounds may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug

release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given in forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc. administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administrations are preferred.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticulare, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, intravenous, intracerebroventricular and subcutaneous doses of the compounds of this invention for a patient, when used for the indicated analgesic effects, will range from about 0.0001 to about 100 mg per kilogram of body weight per day.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical formulation (composition).

In another aspect, the present invention provides pharmaceutically acceptable compositions which comprise a therapeutically-effective amount of one or more of the subject compounds, as described above, formulated together with one or more

pharmaceutically acceptable carriers (additives) and/or diluents. As described in detail below, the pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular or intravenous injection as, for example, a sterile solution or suspension; (3) topical application, for example, as a cream, ointment or spray applied to the skin, lungs, or oral cavity; or (4) intravaginally or intravectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; or (8) nasally.

The compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other pharmaceuticals.

The term "treatment" is intended to encompass also prophylaxis, therapy and cure.

The patient receiving this treatment is any animal in need, including primates, in particular humans, and other mammals such as equines, cattle, swine and sheep; and poultry and pets in general.

The compound of the invention can be administered as such or in admixtures with pharmaceutically acceptable carriers and can also be administered in conjunction with antimicrobial agents such as penicillins, cephalosporins, aminoglycosides and glycopeptides. Conjunctive therapy, thus includes sequential, simultaneous and separate administration of the active compound in a way that the therapeutical effects of the first administered one is not entirely disappeared when the subsequent is administered.

The addition of the active compound of the invention to animal feed is preferably accomplished by preparing an appropriate feed premix containing the active compound in an effective amount and incorporating the premix into the complete ration.

Alternatively, an intermediate concentrate or feed supplement containing the active ingredient can be blended into the feed. The way in which such feed premixes and complete rations can be prepared and administered are described in reference books (such as "Applied Animal Nutrition", W.H. Freedman and CO., San Francisco, U.S.A., 1969 or "Livestock Feeds and Feeding" O and B books, Corvallis, Ore., U.S.A., 1977).

Biological Assays

PPAR Isoform Selectivity.

Chimeric GAL4-PPAR-dependent reporter gene assays were used to determine PPAR isoform selectivity of the tested ligands. The GAL4-PPAR plasmid is a fusion protein of amino acids 1-76 of the glucocorticoid receptor fused to amino acids 1-147 of the yeast transcription factor GAL4 DNA-binding domain, which is fused C-terminally to either amino acids 167-468, 138-440 and 174-475 of the murine PPARα, δ or γ ligand-binding domain (Figure 16). These constructs have been kindly provided by Dr. Steven Kliewer, SmithKlineGlaxo. Lehmann, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkison, W. O.; Willson, T. M. et al., *J Biol Chem* 1995, *270*, 12953-12956.

The chimeric receptor plasmid was cotransfected with a firefly luciferase reporter plasmid containing five copies of the GAL4 UAS response element upstream to the tk promoter. Lehmann, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkison, W. O.; Willson, T. M. et al., *J Biol Chem* 1995, *270*, 12953-12956. Upon binding of the PPAR ligand to the receptor, GAL4-PPAR binds to the UAS elements and activates transcription of the luciferase reporter gene. Luciferase activity was determined using the Dual Luciferase Assay (Promega), which measures the activity of firefly luciferase as well as *Renilla* luciferase that is cotransfected with the PPAR receptor and firefly luciferase plasmids to correct for transfection efficiency. CV-1 monkey kidney cells were grown in 24-well plates in DMEM medium containing 10% delipidated fetal calf serum (Sigma-Aldrich Chemical Co.) and transfected using Lipofectamine (Invitrogen) with 10 ng of PPAR receptor plasmid, 100 ng of firefly luciferase plasmid, and 10 ng of *Renilla* luciferase plasmid. Lehmann, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkison, W. O.; Willson, T. M. et al., *J Biol Chem* 1995, *270*, 12953-12956. The test ligand was added 24 hr after transfection at a concentration of 5 μM in DMSO so that the final concentration of DMSO is 0.1%, a concentration that is noncytotoxic. Luciferase activity was read 24 hr after drug addition. The PPAR agonist standards, WY14643 (Wyeth), L-165041 (Merck) and GW7845 (SmithKlineGlaxo) were included in their respective assays at 5 μM as positive controls for PPARα, δ and γ (Figure 17). The advantage of this assay is that it measures PPAR-dependent transcriptional activation independently of interfering endogenous PPAR activity. Henke, B. R.; Blanchard, S. G.; Brackeen, M. F.; Brown, K. K.; Cobb, J. E. et al.,

J Med Chem 1998, *41*, 5020-5036; Willson, T. M.; Cobb, J. E.; Cowan, D. J.; Wiethe, R. W.; Correa, I. D. et al., *J Med Chem* 1996, *39*, 665-668.

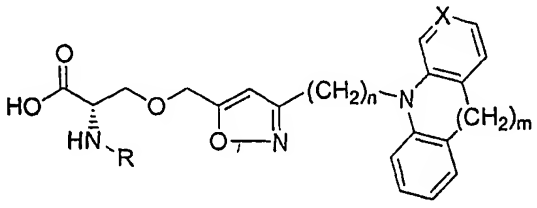
A second assay will measure adipogenesis by determining the ability of 3T3-L1 preadipocytes to undergo adipocyte differentiation in response to the test ligand. Lehmann, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkison, W. O.; Willson, T. M. et al., *J Biol Chem* 1995, *270*, 12953-12956. Cells will be grown in 24-well plates in DMEM supplemented with 10% fetal calf serum. Test PPAR ligands will be added in DMSO as described above and cells will be stained after 7 days with Oil Red O and photographed. Oil Red O staining will also be quantitated by solubilizing the stain in ethanol and reading the absorbance at 550 nm.

Exemplification

The invention now being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

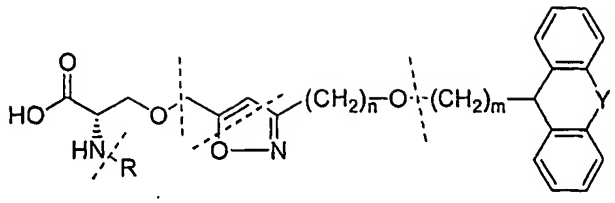
Example 1

Isoxazolyl-serine/cysteine-based ligands - *De novo*/rational design



R = CH_3, SO_2CH_3, SO_2Ph
X = CH, N
n = 1-8
m = 0-2

Cmpd	Structure	PMF score	Pockets occupied
1.	n = 8, m = 0, X = CH, R = CH_3	-62	U1, M, U3
2.	n = 7, m = 0, X = CH, R = CH_3	-77	U1, M, U3
3.	n = 6, m = 0, X = CH, R = CH_3	-45	U1, M, U3
4.	n = 5, m = 0, X = CH, R = CH_3	-82	U1, M, U2, U3
5.	n = 5, m = 0, X = CH, R = SO_2CH_3	-98	L1, U1, M, U2, U3
6.	n = 5, m = 0, X = CH, R = SO_2Ph	-74	U3, U2, M, U1 (COO^- not in U1)
7.	n = 4, m = 0, X = CH, R = CH_3	-51	U1, M, U2, U3
8.	n = 3, m = 2, X = CH, R = CH_3	-60	U2, U3
9.	n = 3, m = 1, X = CH, R = CH_3	-37	U2, U3
10.	n = 3, m = 0, X = CH, R = CH_3	-77	U1, M, U2
11.	n = 3, m = 0, X = CH, R = SO_2CH_3	-94	L1, U1, M, U2, U3
12.	n = 3, m = 0, X = CH, R = SO_2Ph	-99	L1, U1, M, U2, U3
13.	n = 3, m = 0, X = N, R = CH_3	-89	U1, M, U2
14.	n = 3, m = 0, X = N, R = SO_2CH_3	-91	L1, U1, M, U2
15.	n = 3, m = 0, X = N, R = SO_2Ph	-106	L1, U1, M, U2
16.	n = 3, m = 0, X = N, R = COPh	-51	U3, M, U1, L1 (COO^- not in U1)
17.	n = 3, m = 0, X = N, R = $COCH_3$	-103	U1, M, U2, L2
18.	n = 3, m = 0, X = N, R = CH_3, tetrazole in place of acid	-79	U1, M, U2, U3 (tetrazole$^-$ not in U1)
19.	n = 3, m = 0, X = N, R = CH_2Ph	-32	U2, U3
20.	n = 2, m = 0, X = CH, R = CH_3	-51	U2, U3
21.	n = 1, m = 0, X = CH, R = CH_3	-49	U1, M, U2

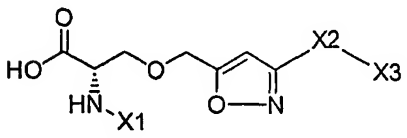


R = CH_3
Y = O, single bond
n = 1,2
m = 0,1,2

Cmpd	Structure	PMF score	Pockets occupied
1	n = 3, m = 0, Y = single bond	-65	U1, M, U3
2	n = 3, m = 0, Y = O	-41	U2, U3
3	n = 2, m = 1, Y = single bond	-75	U2, U3
4	n = 2, m = 0, Y = single bond	-54	U2, U3
5	n = 2, m = 0, Y = O	-65	U2, U3
6	n = 1, m = 2, Y = single bond	-49	U2, U3
7	n = 1, m = 1, Y = single bond	-63	U2, U3

Example 2

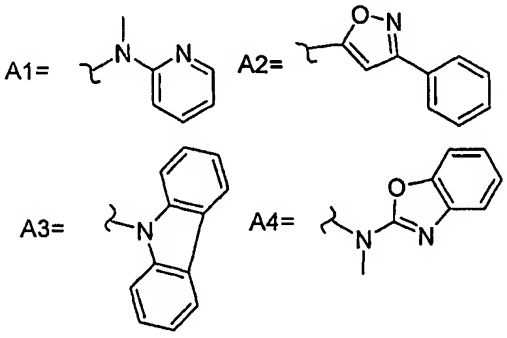
Isoxazolyl-serine/cysteine-based ligands - Virtual combinatorial libraries



X1 = benzyl, SO_2Me, SO_2Ph

X2 = 2-6 carbon spacer with single trans-double bond in positions 1-4

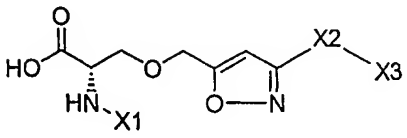
X3 =



Cmpd	Structure	PMF score
1.	X1 = SO_2Me, X2 = $(CH_2)_6$, X3 = A4	-116
2.	X1 = benzyl, X2 = $(CH2)_6$, X3 = A3	-116
3.	X1 = benzyl, X2 = (E)CH=CH$(CH_2)_4$, X3 = A1	-110
4.	X1 = benzyl, X2 = (E)CH=CH$(CH_2)_4$, X3 = A2	-115
5.	X1 = benzyl, X2 = (E)CH=CH$(CH_2)_4$, X3 = A4	-108
6.	X1 = benzyl, X2 = (E)CH=CH$(CH_2)_4$, X3 = A3	-107
7.	X1 = benzyl, X2 = $(CH2)_5$, X3 = A3	-115
8.	X1 = SO_2Me, X2 = $(CH_2)_5$, X3 = A4	-106
9.	X1 = benzyl, X2 = (E)CH=CH$(CH_2)_3$, X3 = A2	-120
10.	X1 = benzyl, X2 = (E)CH=CH$(CH_2)_3$, X3 = A3	-115
11.	X1 = benzyl, X2 = $(CH_2)_4$, X3 = A3	-111
12.	X1 = SO_2Me, X2 = $(CH_2)_4$, X3 = A4	-107
13.	X1 = benzyl, X2 = (E)CH=CH$(CH_2)_2$, X3 = A2	-119
14.	X1 = benzyl, X2 = $(CH_2)_2$(E)CH=CH, X3 = A3	-119
15.	X1 = benzyl, X2 = (E)CH=$CHCH_2$, X3 = A2	-117
16.	X1 = SO_2Me, X2 = $(CH_2)_3$, X3 = A4	-115
17.	X1 = SO_2Me, X2 = $(CH_2)_2$, X3 = A4	-109
18.	X1 = benzyl, X2 = (E)CH=CH, X3 = A1	-124
19.	X1 = benzyl, X2 = (E)CH=CH, X3 = A4	-117
20.	X1 = benzyl, X2 = (E)CH=CH, X3 = A1	-116
21.	X1 = benzyl, X2 = (E)CH=CH, X3 = A2	-109

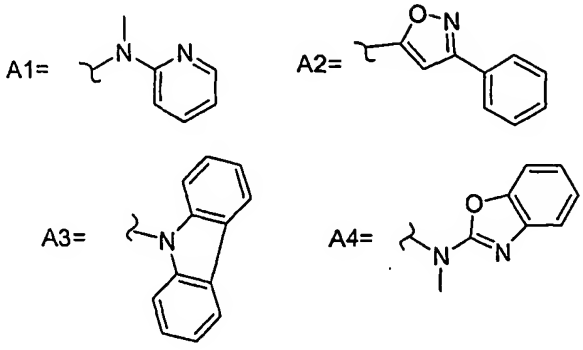
Example 3

Isoxazolyl-serine/cysteine-based ligands - Virtual combinatorial libraries



X1 = benzyl, SO_2Me, SO_2Ph

X2 = 2-6 carbon spacer with one OH group in positions 1-6, stereochemistry assigned by CONCORD and was not controlled

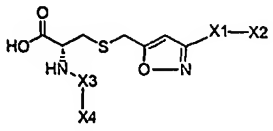


numbering for X2 starts from isoxazole ring

Cmpd	Structure	PMF score
1.	X1 = benzyl, X2 = 1-OH-hexyl, X3 = A1	-104
2.	X1 = benzyl, X2 = 2-OH-hexyl, X3 = A1	-110
3.	X1 = SO_2Me, X2 = 4-OH-hexyl, X3 = A4	-104
4.	X1 = SO_2Ph, X2 = 4-OH-hexyl, X3 = A1	-104
5.	X1 = benzyl, X2 = 4-OH-hexyl, X3 = A1	-103
6.	X1 = SO_2Me, X2 = 4-OH-pentyl, X3 = A1	-102
7.	X1 = SO_2Me, X2 = 2-OH-butyl, X3 = A4	-110
8.	X1 = benzyl, X2 = 3-OH-butyl, X3 = A1	-112
9.	X1 = benzyl, X2 = 1-OH-propyl, X3 = A1	-112
10.	X1 = SO_2Me, X2 = 3-OH-propyl, X3 = A1	-104
11.	X1 = SO_2Me, X2 = 1-OH-ethyl, X3 = A1	-106

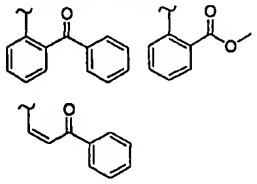
Example 4

Isoxazolyl-serine/cysteine-based ligands - Virtual combinatorial libraries



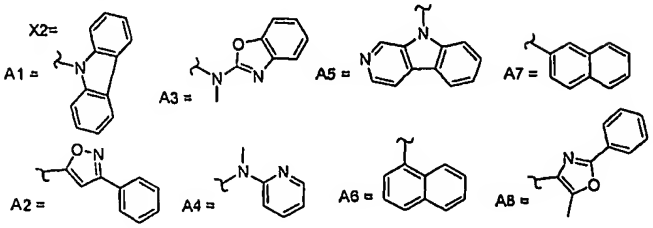
when X3 = $(CH2)_m$, m= 1-5
X4 = *p*-, *m*-, *o*-substituted phenyl ring with the following substitutuents Me, CH_2OH, NO_2, $CONH_2$, NHCHO, F, NH_2, I, CF_3, OEt, H

when X3 = nothing
X4 = SO_2Me, SO_2Ph, Ac, Boc, Cbz,Bsmoc



X1 = (CH2)n, n = 5,6

X2=



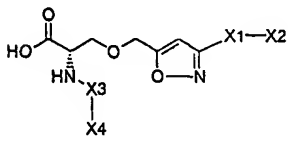
X2 = *p*-, *m*-, *o*-substituted phenyl ring with the following substitutuents Me, CH_2OH, NO_2, $CONH_2$, NHCHO, F, NH_2, I, CF_3, OEt, H

5

Cmpd	Structure	PMF score
1.	X1 = $(CH_2)_6$, X2 = A2, X3 = $(CH_2)_4$, X4 = *p*-NHCHO-Ph	-110
2.	X1 = $(CH_2)_6$, X2 = A8, X3 = $(CH_2)_4$, X4 = *p*-$CONH_2$-Ph	-117
3.	X1 = $(CH_2)_6$, X2 = A8, X3 = $(CH_2)_4$, X4 = *o*-NO_2-Ph	-109
4.	X1 = $(CH_2)_6$, X2 = A2, X3 = $(CH_2)_3$, X4 = *o*-NHCHO-Ph	-118
5.	X1 = $(CH_2)_6$, X2 = A8, X3 = $(CH_2)_2$, X4 = *p*-$CONH_2$-Ph	-109
6.	X1 = $(CH_2)_6$, X2 = A8, X3 = $(CH_2)_2$, X4 = *p*-OEt-Ph	-109
7.	X1 = $(CH_2)_6$, X2 = A5, X3 = $(CH_2)_2$, X4 = *m*-OEt-Ph	-110
8.	X1 = $(CH_2)_6$, X2 = A2, X3 = nothing, X4 = CO_2CH_2Ph	-115
9.	X1 = $(CH_2)_6$, X2 = A8, X3 = nothing, X4 = CO_2CH_2Ph	-120
10.	X1 = $(CH_2)_6$, X2 = A6, X3 = nothing, X4 = Bsmoc	-115
11.	X1 = $(CH_2)_6$, X2 = A7, X3 = nothing, X4 = Bsmoc	-109
12.	X1 = $(CH_2)_6$, X2 = A5, X3 = nothing, X4 = Bsmoc	-118
13.	X1 = $(CH_2)_5$, X2 = A5, X3 = $(CH_2)_4$, X4 = *o*-NHCHO-Ph	-121
14.	X1 = $(CH_2)_5$, X2 = A5, X3 = $(CH_2)_4$, X4 = *m*-CH_2OH-Ph	-114
15.	X1 = $(CH_2)_5$, X2 = A5, X3 = $(CH_2)_4$, X4 = *m*-NHCHO-Ph	-123
16.	X1 = $(CH_2)_5$, X2 = A5, X3 = $(CH_2)_4$, X4 = *p*-NHCHO-Ph	-114
17.	X1 = $(CH_2)_5$, X2 = A5, X3 = $(CH_2)_4$, X4 = *o*-CH_2OH-Ph	-114
18.	X1 = $(CH_2)_5$, X2 = A4, X3 = $(CH_2)_4$, X4 = *o*-NHCHO -Ph	-111
19.	X1 = $(CH_2)_5$, X2 = A5, X3 = $(CH_2)_3$, X4 = *o*-NHCHO-Ph	-114
20.	X1 = $(CH_2)_5$, X2 = A1 X3 = $(CH_2)_2$, X4 = *p*-F-Ph	-108
21.	X1 = $(CH_2)_5$, X2 = A1 X3 = $(CH_2)_2$, X4 = *p*-CF_3-Ph	-111
22.	X1 = $(CH_2)_5$, X2 = A8, X3 = $(CH_2)_2$, X4 = *m*-OEt-Ph	-112
23.	X1 = $(CH_2)_5$, X2 = A4, X3 = nothing, X4 = Bsmoc	-108
24.	X1 = $(CH_2)_5$, X2 = A8, X3 = nothing, X4 = CO_2CH_2Ph	-111
25.	X1 = $(CH_2)_5$, X2 = A7, X3 = nothing, X4 = Bsmoc	-112

Example 5

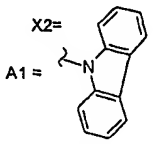
Isoxazolyl-serine/cysteine-based ligands - Virtual combinatorial libraries



X1 = $(CH_2)_n$, n = 3, 5

X2=

A1 =



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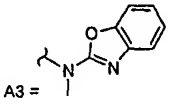
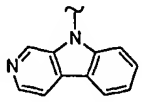
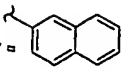


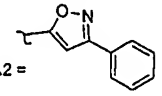
A5 =



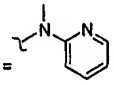
A7 =



A2 =

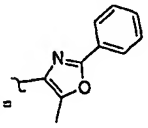


A4 =



A6 =

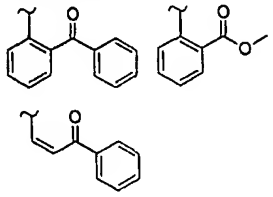
A8 =



when X3 = $(CH_2)_m$, m= 1-4
X4 = *p*-, *m*-, o-substituted phenyl ring with the following substitutuents Me, CH_2OH, NO_2, $CONH_2$, NHCHO, F, NH_2, I, CF_3, OEt, H

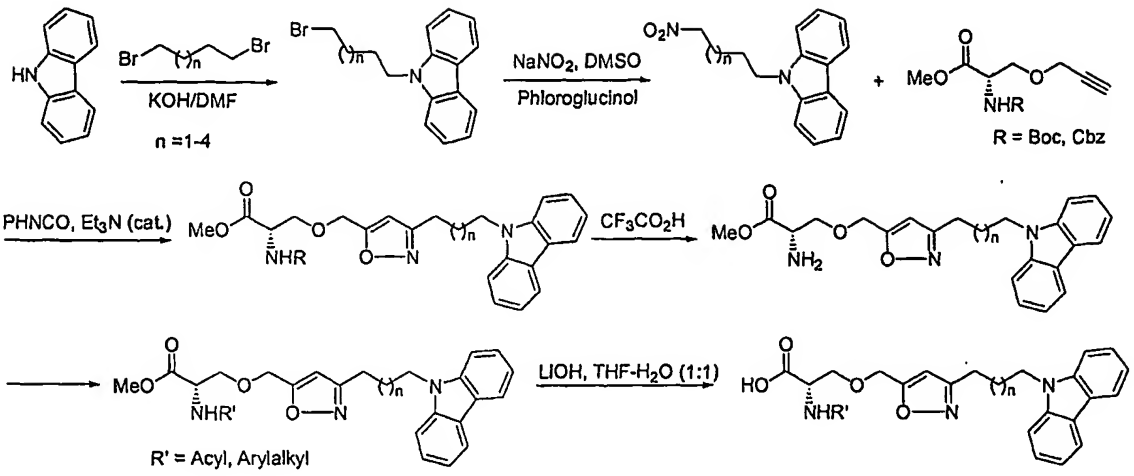
X2 = *p*-, *m*-, o-substituted phenyl ring with the following substitutuents Me, CH_2OH, NO_2, $CONH_2$, NHCHO, F, NH_2, I, CF_3, OEt, H
in general, all substituent from Hansch cluster will be considered

when X3 = nothing
X4 = SO_2Me, SO_2Ph, Ac, Boc, Cbz,Bsmoc



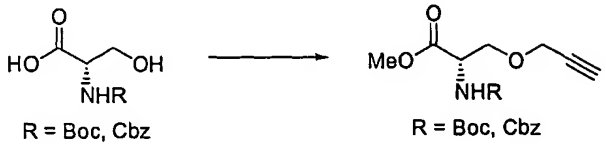
Cmpd	Structure	PMF score
1.	X1 = $(CH_2)_5$, X2 = A7, X3 = $(CH_2)_3$, X4 = *o*-$CONH_2$-Ph	-141
2.	X1 = $(CH_2)_5$, X2 = A7, X3 = $(CH_2)_3$, X4 = *o*-NHCHO-Ph	-140
3.	X1 = $(CH_2)_5$, X2 = A5, X3 = $(CH_2)_2$, X4 = *m*-NHCHO-Ph	-138
4.	X1 = $(CH_2)_5$, X2 = A4, X3 = $(CH_2)_2$, X4 = *p*-$CONH_2$-Ph	-137
5.	X1 = $(CH_2)_5$, X2 = A6, X3 = $(CH_2)_2$, X4 = *m*-NHCHO-Ph	-138
6.	X1 = $(CH_2)_5$, X2 = A6, X3 = $(CH_2)_2$, X4 = *p*-$CONH_2$-Ph	-141
7.	X1 = $(CH_2)_5$, X2 = A6, X3 = $(CH_2)_2$, X4 = *p*-OEt-Ph	-136
8.	X1 = $(CH_2)_3$, X2 = A4, X3 = $(CH_2)_3$, X4 = *o*-NO_2-Ph	-137
9.	X1 = $(CH_2)_3$, X2 = A4, X3 = $(CH_2)_3$, X4 = *o*-$CONH_2$-Ph	-138
10.	X1 = $(CH_2)_3$, X2 = A4, X3 = $(CH_2)_3$, X4 = *m*-$CONH_2$-Ph	-137
11.	X1 = $(CH_2)_3$, X2 = A6, X3 = $(CH_2)_3$, X4 = *o*-$CONH_2$-Ph	-140
12.	X1 = $(CH_2)_3$, X2 = A7, X3 = $(CH_2)_3$, X4 = *o*-NO_2-Ph	-137
13.	X1 = $(CH_2)_3$, X2 = A7, X3 = $(CH_2)_3$, X4 = *o*-$CONH_2$-Ph	-138
14.	X1 = $(CH_2)_3$, X2 = A7, X3 = $(CH_2)_3$, X4 = *o*-NHCHO-Ph	-138
15.	X1 = $(CH_2)_3$, X2 = A4, X3 = $(CH_2)_2$, X4 = *m*-$CONH_2$-Ph	-138
16.	X1 = $(CH_2)_3$, X2 = A4, X3 = $(CH_2)_2$, X4 = *p*-$CONH_2$-Ph	-136
17.	X1 = $(CH_2)_3$, X2 = A4, X3 = $(CH_2)_2$, X4 = *p*-NHCHO-Ph	-137
18.	X1 = $(CH_2)_3$, X2 = A4, X3 = $(CH_2)_2$, X4 = *p*-OEt-Ph	-136
19.	X1 = $(CH_2)_3$, X2 = A8, X3 = $(CH_2)_2$, X4 = *p*-OEt-Ph	-136
20.	X1 = $(CH_2)_3$, X2 = A6, X3 = $(CH_2)_2$, X4 = *m*-NHCHO-Ph	-138
21.	X1 = $(CH_2)_3$, X2 = A6, X3 = $(CH_2)_2$, X4 = *m*-$CONH_2$-Ph	-140
22.	X1 = $(CH_2)_3$, X2 = A5, X3 = $(CH_2)_2$, X4 = *p*-$CONH_2$-Ph	-139
23.	X1 = $(CH_2)_3$, X2 = A5, X3 = $(CH_2)_2$, X4 = *p*-NH_2-Ph	-140
24.	X1 = $(CH_2)_3$, X2 = A6, X3 = CH_2, X4 = *p*-NHCHO-Ph	-138
25.	X1 = $(CH_2)_3$, X2 = A6, X3 = CH_2, X4 = *p*-OEt-Ph	-136

Scheme 11. Synthetic Scheme



5

Example 6



10 General Procedure

To a stirred solution of Boc or Cbz protected L-serine (25 mmol) in DMF (150 mL) at 0 °C was added carefully NaH (60% in mineral oil, 4.0 g, 100 mmol). After that the reaction mixture was stirred for 30 min until hydrogen evolution stopped. Propargyl bromide (4.46 mL, 50 mmol) was added, and the mixture was stirred at 0 °C for 30 min and 15 then room temperature for 12 h; MeI (2.40 mL) was added. Two hours later the reaction mixture was poured into brine, and extracted with ether (150 mL × 3). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography with hexane-ether (4:1).

20

R = Cbz:

Yield, 41%; viscous oil; $[\alpha]_D$ +13.5 (c 1.6, $CHCl_3$)

^{1}H NMR ($CDCl_3$) δ 7.37-7.26 (m, 5H), 5.66 (d, 1H, J = 8.7 Hz), 5.12 (s, 2H), 4.53 (dt, 1H, J = 8.7, 3.0 Hz), 4.13 (d, 2H, J = 2.4 Hz), 3.97 (dd, 1H, J = 9.3, 3.0 Hz), 3.78 (dd, 1H, J = 9.3, 3.3 Hz), 3.76 (s, 3H), 2.42 (t, 1H, J = 2.4 Hz).

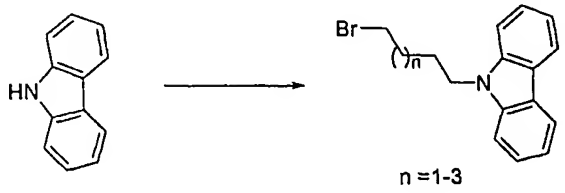
R = Boc:

Yield, 39%, viscous oil. $[\alpha]_D$ +17.8 (c 2.7, $CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 5.38 (d, 1H, J = 8.4 Hz), 4.46 (dt, 1H, J = 8.4, 3.3 Hz), 4.15 (d, 2H, J = 2.4 Hz), 3.96 (dd, 1H, J = 9.3, 3.3 Hz), 3.77 (s, 3H), 3.76 (dd, 1H, J = 9.3, 3.3 Hz), 2.46 (t, 1H, J = 2.4 Hz), 1.46 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 170.86, 155.40, 79.98, 78.77, 75.03, 69.61, 58.49, 53.72, 52.49, 28.24.

Example 7



General procedure

A mixture of 10 g (60 mmol) of carbazole, KOH (3.5 g, 60 mmol), dibromoalkane (180 mmol) in DMF (200 mL) was stirred at room temperature for two days. The reaction mixture was diluted with water (300 mL), and extracted with ether (150 mL × 3). The combined organic layers were washed with brine, dried (MgSO4), and concentrated. The residue was purified by chromatography with hexane-CH_2Cl_2 (4:1) to give the desired product.

n = 1:

Yield, 76%; white solid.

^{1}H NMR ($CDCl_3$) δ 8.10 (d, 2H, J = 7.8 Hz), 7.50-7.38 (m, 4H), 7.27-7.21 (m, 2H), 4.35 (t, 2H, J = 6.9 Hz), 3.38 (t, 2H, J = 6.6 Hz), 2.12-2.00 (m, 2H), 1.95-1.86 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 140.25, 125.70, 122.87, 120.41, 118.93, 108.50, 42.14, 33.14, 30.22, 27.64.

n = 2:

Yield, 78%; white solid.

^{1}H NMR ($CDCl_3$) δ 8.08 (d, 2H, J = 7.8 Hz), 7.47-7.33 (m, 4H), 7.24-7.18 (m, 2H), 4.24 (t, 2H, J = 6.9 Hz), 3.28 (t, 2H, J = 6.9 Hz), 1.88-1.75 (m, 4H), 1.52-1.40 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 140.24, 125.60, 122.77, 120.33, 118.78, 108.50, 42.68, 33.30, 32.37, 28.08, 25.80.

n = 3:

Yield, 80%; white solid.

^{1}H NMR ($CDCl_3$) δ 8.09 (d, 2H, J = 7.8 Hz), 7.48-7.34 (m, 4H), 7.24-7.18 (m, 2H), 4.26 (t, 2H, J = 6.9 Hz), 3.31 (t, 2H, J = 6.9 Hz), 1.90-1.71 (m, 4H), 1.50-1.25 (m, 2H).

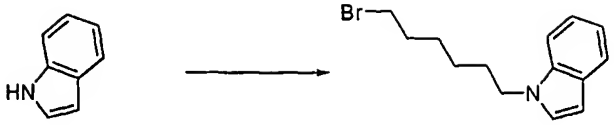
^{13}C NMR ($CDCl_3$) δ 140.31, 125.56, 122.75, 120.31, 118.72, 108.54, 42.76, 33.72, 32.50, 28.76, 27.85, 26.39.

n = 4:

Yield, 83%; colorless viscous oil.

^{1}H NMR ($CDCl_3$) δ 8.08 (d, 2H, J = 7.8 Hz), 7.48-7.35 (m, 4H), 7.24-7.18 (m, 2H), 4.25 (t, 2H, J = 7.2 Hz), 3.32 (t, 2H, J = 6.9 Hz), 1.89-1.71 (m, 4H), 1.40-1.23 (m, 6H).

^{13}C NMR ($CDCl_3$) δ 140.32, 125.54, 122.74, 120.30, 118.69, 108.56, 42.88, 33.83, 32.58, 28.80, 28.49, 27.92, 27.05.

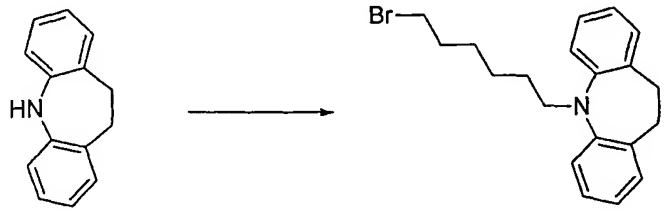


Yield, 83%; colorless oil.

^{1}H NMR ($CDCl_3$) δ 7.63 (d, 1H, J = 8.1 Hz), 7.33 (d, 1H, J = 7.8 Hz), 7.23-7.06 (m, 3H), 6.48 (d, 1H, J = 3.3 Hz), 4.10 (t, 2H, J = 7.2 Hz), 3.35 (t, 2H, J = 6.9 Hz), 1.89-1.75 (m, 4H), 1.50-1.25 (m, 4H).

^{13}C NMR ($CDCl_3$) δ 135.85, 128.51, 127.71, 121.30, 120.92, 119.16, 109.27, 100.91, 46.14, 33.70, 32.50, 30.02, 27.70, 26.09.

Example 8

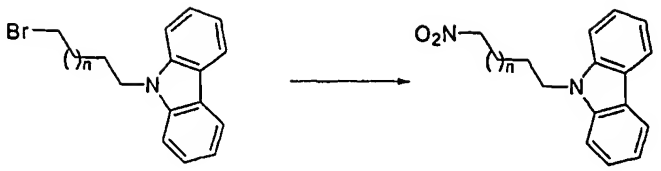


To a stirred solution of iminodibenzyl (10 g, 51 mmol) in DMF (150 mL) at 0 °C was added NaH (60% in mineral oil, 2.45 g, 61 mmol) in portions. The mixture was stirred at 0 °C for 30 min and then warmed to 60 °C for 1 h. After cooled to 0 °C, 1,6-dibromohexane (20 mL, 123 mmol) was added. The reaction was stirred at room temperature overnight and then at 60 °C for two days. After that the reaction mixture was poured into an ice cold water (300 mL) and extracted with ethyl acetate (100 mL × 4). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography with hexane-CH_2Cl_2-Et_2O (5:1:1) to give the desired product (7.5 g, 41%).

^{1}H NMR ($CDCl_3$) δ 7.14-7.02 (m, 6H), 6.92-6.86 (m, 2H), 3.70 (t, 2H, J = 6.9 Hz), 3.30 (t, 2H, J = 6.9 Hz), 3.14 (s, 4H), 1.80-1.70 (m, 2H), 1.60-1.50 (m, 2H), 1.40-1.25 (m, 4H).

^{13}C NMR ($CDCl_3$) δ 148.27, 134.12, 129.72, 126.22, 122.26, 119.89, 50.41, 33.73, 32.58, 32.16, 27.74, 27.61, 26.20.

Example 9



General procedure

Bromide (17.6 mmol) in DMSO (10 mL) was added to a mixture of $NaNO_2$ (3.01 g, 43.6 mmol) and phloroglucinol (3.55 g, 21.9 mmol) in DMSO (10 mL). The reaction mixture was stirred at room temperature for 48 h. After quenching of the reaction with ice-cold water (100 mL), the aqueous layer was extracted with EtOAc (50 mL × 4) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography with hexane-CH_2Cl_2-Et_2O (4:1:1) to give the desired product.

n = 1

Yield, 57%; white solid.

^1H NMR ($CDCl_3$) δ 8.11 (d, 2H, J = 7.8 Hz), 7.51-7.64 (m, 4H), 7.28-7.22 (m, 2H), 4.39 (t, 2H, J = 6.3 Hz), 4.32 (t, 2H, J = 6.3 Hz), 2.10-1.94 (m, 4H).

^{13}C NMR ($CDCl_3$) δ 140.17, 125.84, 122.94, 120.51, 119.14, 108.38, 75.11, 42.01, 25.88, 25.05.

n = 2

Yield, 61%; syrup.

^1H NMR ($CDCl_3$) δ 8.09 (d, 2H, J = 7.8 Hz), 7.48-7.32 (m, 4H), 7.25-7.19 (m, 2H), 4.27 (t, 2H, J = 6.9 Hz), 4.24 (t, 2H, J = 6.9 Hz), 1.99-1.83 (m, 4H), 1.46-1.34 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 140.20, 125.68, 122.79, 120.39, 118.92, 108.43, 75.15, 42.45, 28.26, 27.03, 23.97.

n = 3

Yield, 59%; syrup.

^{1}H NMR ($CDCl_3$) δ 8.06 (d, 2H, J = 7.8 Hz), 7.45-7.16 (m, 6H), 4.17 (t, 2H, J = 6.9 Hz), 4.15 (t, 2H, J = 6.9 Hz), 1.84-1.71 (m, 4H), 1.35-1.15 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 140.19, 125.56, 122.66, 120.25, 118.74, 108.47, 75.25, 42.49, 28.49, 26.93, 26.37, 25.86.

n = 4

Yield, 64%; syrup.

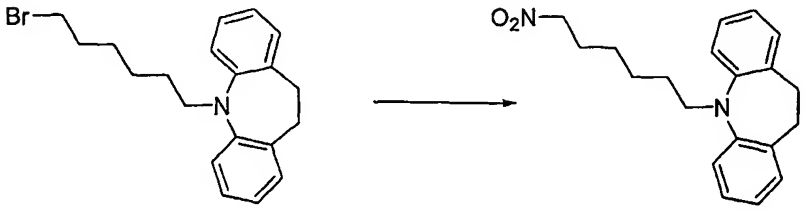
^{1}H NMR ($CDCl_3$) δ 8.09 (d, 2H, J = 7.8 Hz), 7.49-7.36 (m, 4H), 7.25-7.19 (m, 2H), 4.29 (t, 4H, J = 6.9 Hz), 1.97-1.81 (m, 4H), 1.45-1.25 (m, 6H).

^{13}C NMR ($CDCl_3$) δ 140.33, 125.58, 122.77, 120.34, 118.75, 108.55, 75.49, 42.84, 28.76, 28.61, 27.17, 26.93, 26.04.

Yield, 60%; syrup.

^{1}H NMR ($CDCl_3$) δ 7.61 (d, 1H, J = 7.8 Hz), 7.29 (d, 1H, J = 8.1 Hz), 7.21-7.05 (m, 2H), 7.03 (d, 1H, J = 3.0 Hz), 6.46 (dd, 1H, J = 3.0, 0.6 Hz), 4.23 (t, 2H, J = 6.9 Hz), 4.05 (t, 2H, J = 6.9 Hz), 1.93-1.73 (m, 4H), 1.37-1.20 (m, 4H).

^{13}C NMR ($CDCl_3$) δ 135.76, 128.46, 127.64, 121.28, 120.86, 119.13, 109.19, 100.91, 75.30, 45.92, 29.74, 26.99, 26.09, 25.73.

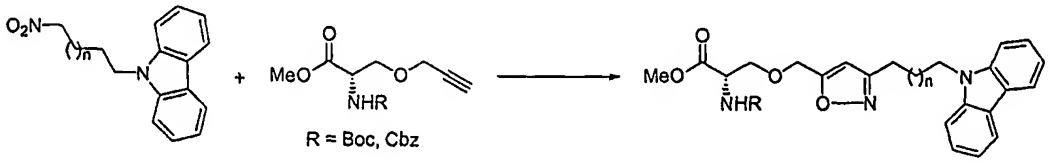


Yield, 54%; syrup.

^{1}H NMR ($CDCl_3$) δ 7.14-7.02 (m, 6H), 6.90-6.87 (m, 2H), 4.24 (t, 2H, J = 7.2 Hz), 3.70 (t, 2H, J = 6.9 Hz), 3.14 (s, 4H), 1.94-1.83 (m, 2H), 1.60-1.50 (m, 2H), 1.40-1.22 (m, 4H).

^{13}C NMR ($CDCl_3$) δ 148.18, 134.12, 129.74, 126.25, 122.33, 119.85, 75.38, 50.22, 32.12, 27.39, 27.13, 26.24, 25.79.

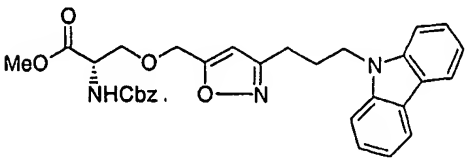
Example 10



General procedure

Nitro compound (1.6 mmol), L-serine derivative (1.6 mmol), and phenyl isocyanate (350 μL, 3.2 mmol) were dissolved in toluene (25 mL). Triethylamine (50 μL) was added and the reaction mixture was refluxed at 120 °C for 24 h under N_2. After cooled to room temperature, the reaction was quenched with 10 drops of water, and the mixture was stirred for an additional 1 h. The solid was removed by filtration, and the filtrate was concentrated. The residue was purified by chromatography with hexane-EtOAc (3:1) to give the isoxazole.

n = 1, R = Cbz:

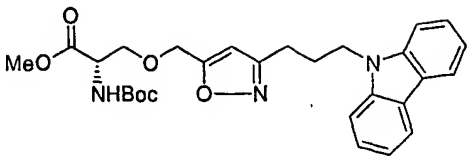


Yield, 67%; light yellow foam; $[\alpha]_D$ +6.5 (c 2.2, $CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 8.08 (d, 2H, J = 7.8 Hz), 7.47-7.18 (m, 11H), 5.91 (s, 1H), 5.63 (d, 1H, J = 8.4 Hz), 5.09 (s, 2H), 4.55-4.45 (m, 1H), 4.52 and 4.46 (AB quart, 2H, J =13.8 Hz), 4.37 (t, 2H, J = 6.9 Hz), 3.91 (dd, 1H, J = 9.6, 2.7 Hz), 3.73 (m, 1H), 3.70 (s, 3H), 2.66 (t, 2H, J = 7.2 Hz), 2.30-2.19 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 170.25, 168.12, 162.72, 155.83, 140.19, 136.02, 128.44, 128.12, 128.00, 125.64, 122.78, 120.28, 118.89, 108.50, 102.73, 70.58, 67.01, 63.91, 54.14, 52.61, 41.99, 26.85, 23.72.

n = 1, R = Boc:

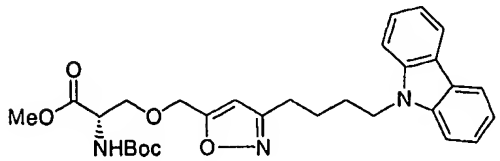


Yield, 61%; syrup; $[\alpha]_D$ +14.3 (c 1.4, $CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 8.09 (d, 2H, *J* = 7.8 Hz), 7.48-7.35 (m, 4H), 7.25-7.19 (m, 2H), 5.94 (s, 1H), 5.37 (d, 1H, *J* = 8.7 Hz), 4.55 and 4.49 (AB quart, 2H, *J* = 13.8 Hz), 4.45 (m, 1H), 4.39 (t, 2H, *J* = 6.9 Hz), 3.90 (dd, 1H, *J* = 9.3, 3.0 Hz), 3.72 (dd, 1H, *J* = 9.3, 3.6 Hz), 3.71 (s, 3H), 2.68 (t, 2H, *J* = 7.5 Hz), 2.32-2.21 (m, 2H), 1.43 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 170.64, 168.25, 162.72, 155.31, 140.21, 125.65, 122.79, 120.29, 118.90, 108.50, 102.68, 80.08, 70.81, 63.95, 53.74, 52.51, 42.01, 28.19, 26.87, 23.75.

n = 2, R = Boc:



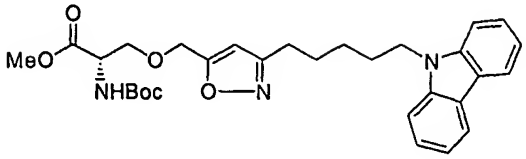
Yield, 79%; syrup; $[\alpha]_D$ +9.6 (c 1.7, $CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 8.09 (d, 2H, *J* = 7.8 Hz), 7.48-7.36 (m, 4H), 7.25-7.19 (m, 2H), 5.88 (s, 1H), 5.36 (d, 1H, *J* = 8.7 Hz), 4.52 and 4.46 (AB quart, 2H, *J* = 13.8 Hz), 4.47-4.41 (m, 1H), 4.32 (t, 2H, *J* = 6.9 Hz), 3.88 (dd, 1H, *J* = 9.6, 3.0 Hz), 3.71 (dd, 1H, *J* = 9.6, 3.3 Hz), 3.70 (s, 3H), 2.64 (t, 2H, *J* = 7.2 Hz), 1.99-1.88 (m, 2H), 1.77-1.65 (m, 2H), 1.45 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 170.67, 168.15, 163.16, 155.33, 140.25, 125.59, 122.75, 120.30,

118.79, 108.52, 102.55, 80.09, 70.81, 63.98, 53.75, 52.49, 42.43, 28.26, 28.22, 25.65, 25.59.

n = 3, R = Boc:

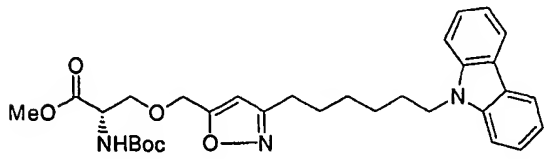


Yield, 70%; syrup; $[\alpha]_D$ +15.1 (c 2.35, $CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 8.10 (d, 2H, J = 7.8 Hz), 7.49-7.37 (m, 4H), 7.25-7.19 (m, 2H), 5.93 (s, 1H), 5.37 (d, 1H, J = 8.4 Hz), 4.54 and 4.49 (AB quart, 2H, J = 13.8 Hz), 4.48-4.40 (m, 1H), 4.30 (t, 2H, J = 7.2 Hz), 3.91 (dd, 1H, J = 9.3, 3.3 Hz), 3.74 (s, 3H), 3.72 (dd, 1H, J = 9.3, 3.3 Hz), 2.59 (t, 2H, J = 7.5 Hz), 1.96-1.85 (m, 2H), 1.72-1.61 (m, 2H), 1.49-1.38 (m, 2H), 1.45 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 170.71, 168.01, 163.49, 155.35, 140.28, 125.57, 122.74, 120.29, 118.73, 108.54, 102.69, 80.12, 70.84, 64.03, 53.78, 52.55, 42.74, 28.55, 28.24, 27.88, 26.75, 25.77.

n = 4, R = Boc:

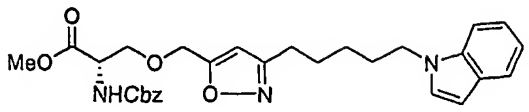


Yield, 35%; syrup.

^{1}H NMR ($CDCl_3$) δ 8.10 (d, 2H, J = 7.8 Hz), 7.49-7.37 (m, 4H), 7.26-7.19 (m, 2H), 5.99 (s, 1H), 5.36 (d, 1H, J = 8.4 Hz), 4.56 and 4.50 (AB quart, 2H, J = 14.1 Hz), 4.48-4.42 (m, 1H), 4.30 (t, 2H, J = 7.2 Hz), 3.92 (dd, 1H, J = 9.3, 3.0 Hz), 3.74 (dd, 1H, J = 9.3, 3.3 Hz), 3.73 (s, 3H), 2.60 (t, 2H, J = 7.5 Hz), 1.93-1.82 (m, 2H), 1.65-1.55 (m, 2H), 1.44 (s, 9H), 1.45-1.37 (m, 4H),

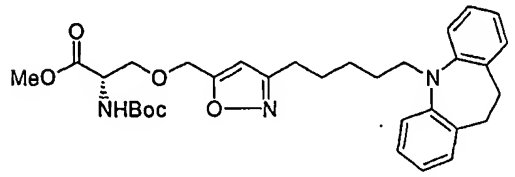
^{13}C NMR ($CDCl_3$) δ 170.72, 168.01, 163.74, 155.36, 140.33, 125.55, 122.74, 120.30,

118.70, 108.57, 102.66, 80.13, 70.87, 64.08, 53.79, 52.55, 42.89, 28.88, 28.83, 28.24, 27.96, 26.94, 25.83.



Yield, 55%; syrup;

^{1}H NMR ($CDCl_3$) δ 7.62 (d, 1H, J = 7.5 Hz), 7.40-7.05 (m, 9H), 6.47 (m, 1H), 5.94 (s, 1H), 5.61 (d, 1H, J = 8.1 Hz), 5.12 (s, 2H), 4.57-4.46 (m, 3H), 4.11 (t, 2H, J = 7.2 Hz), 3.94 (dd, 1H, J = 9.3, 3.3 Hz), 3.76 (dd, 1H, J = 9.3, 3.0 Hz), 3.74 (s, 3H), 2.60 (t, 2H, J = 7.5 Hz), 1.92-1.81 (m, 2H), 1.71-1.60 (m, 2H), 1.42-1.31 (s, 2H).

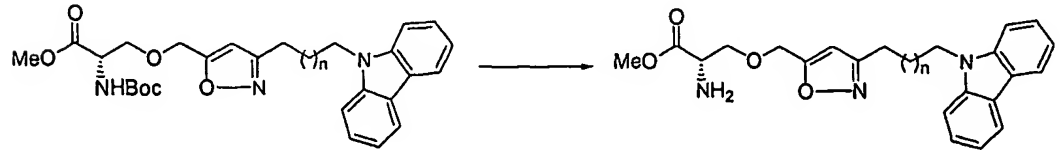


Yield, 36%; syrup; $[\alpha]_D$ +23.8 (c 1.8, $CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 7.15-7.03 (m, 6H), 6.93-6.87 (m, 2H), 5.98 (s, 1H), 5.37 (d, 1H, J = 8.7 Hz), 4.56 and 4.50 (AB quart, 2H, J = 14.1 Hz), 4.48-4.41 (m, 1H), 3.92 (dd, 1H, J = 9.3, 3.3 Hz), 3.78-3.68 (m, 6H), 3.14 (s, 4H), 2.58 (t, 2H, J = 7.5 Hz), 1.65-1.54 (m, 4H), 1.44 (s, 9H), 1.43-1.33 (m, 2H),

^{13}C NMR ($CDCl_3$) δ 170.71, 167.94, 163.74, 155.33, 148.25, 134.15, 129.72, 126.24, 122.29, 119.90, 102.65, 80.11, 70.84, 64.05, 53.78, 52.54, 50.35, 32.13, 28.24, 27.86, 27.49, 26.63, 25.84.

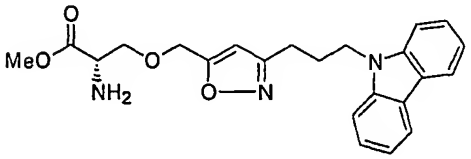
Example 11



General procedure

To a stirred solution of Boc compound (0.73 mmol) in dry CH_2Cl_2 (5 mL) was added trifluoroacetic acid (0.5 mL). The reaction mixture was stirred at room temperature for 3 h. After that the reaction mixture was quenched with saturated aqueous K_2CO_3, and diluted with EtOAc (100 mL). The organic layer was separated and washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography with EtOAc-MeOH (10:1).

n = 1:

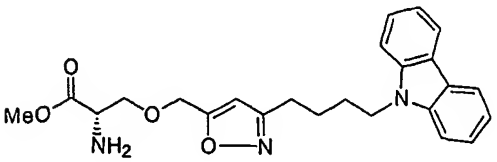


Yield, 95%; syrup; $[\alpha]_D$ + 13.5 (c 1.1, $CHCl_3$).

^1H NMR ($CDCl_3$) δ 8.09 (d, 2H, J = 8.1 Hz), 7.49-7.36 (m, 4H), 7.26-7.20 (m, 2H), 6.00 (s, 1H), 4.57 (s, 2H), 4.41 (t, 2H, J = 6.9 Hz), 3.80-3.72 (m, 2H), 3.71 (s, 3H), 3.65-3.61 (m, 1H), 2.71 (t, 2H, J = 7.5 Hz), 2.34-2.23 (m, 2H), 1.71 (br s, 2H).

^{13}C NMR ($CDCl_3$) δ 173.74, 168.67, 162.79, 140.25, 125.68, 122.84, 120.33, 118.92, 108.54, 102.62, 72.75, 64.05, 54.67, 52.24, 42.08, 26.93, 23.80.

n = 2:

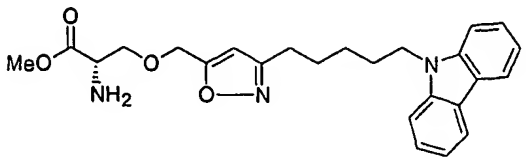


Yield, 98%; syrup; $[\alpha]_D$ +9.8 (c 1.1, MeOH).

^1H NMR ($CDCl_3$) δ 8.09 (d, 2H, J = 8.1 Hz), 7.48-7.36 (m, 4H), 7.25-7.19 (m, 2H), 5.92 (s, 1H), 4.52 (s, 2H), 3.85-3.50 (m, 6H), 2.64 (t, 2H, J = 7.2 Hz), 2.02 (br s, 2H), 1.99-1.88 (m, 2H), 1.77-1.66 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 168.47, 163.20, 140.25, 125.59, 122.75, 120.30, 118.78, 108.53, 102.50, 72.62, 63.99, 54.56, 52.23, 42.45, 28.27, 25.66, 25.60.

n = 3:



Yield, 99%; syrup; $[\alpha]_D$ +5.9 (c 1.5, MeOH).

^1H NMR ($CDCl_3$) δ 8.10 (d, 2H, *J* = 7.8 Hz), 7.49-7.37 (m, 4H), 7.26-7.19 (m, 2H), 5.97 (s, 1H), 4.52 (s, 2H), 4.30 (t, 2H, *J* = 7.2 Hz), 3.77 (dd, 1H, *J* = 9.0, 5.1 Hz), 3.73 (dd, 1H, *J* = 9.0, 3.9 Hz), 3.72 (s, 3H), 3.66-3.62 (m, 1H), 2.60 (t, 2H, *J* = 7.5 Hz), 1.97-1.86 (m, 2H), 1.75-1.62 (m, 2H), 1.71 (br s, 2H), 1.51-1.39 (m, 2H).

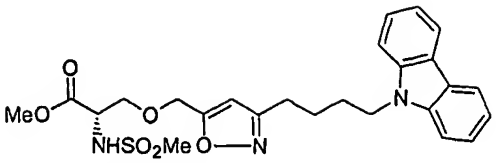
^{13}C NMR ($CDCl_3$) δ 173.79, 168.37, 163.53, 140.29, 125.58, 122.75, 120.30, 118.73, 108.55, 102.61, 72.76, 64.07, 54.69, 52.24, 42.77, 28.57, 27.90, 26.76, 25.80.

Example 12

General procedure

To a stirred solution of amine (0.13 mmol) in CH_2Cl_2 (2 mL) and Et_3N (0.1 mL) at 0 °C was added sulfonyl chloride (20 mmol). The reaction mixture was warmed to room temperature and stirred under N_2 for 12 h. After that, the reaction mixture was quenched with brine, and diluted with EtOAc (50 mL). The organic layer was separated and washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography with hexane-EtOAc (2:1 to 1:1).

R = Me:



Yield, 72%; $[\alpha]_D$ +3.4 (c 1.8, $CHCl_3$).

^1H NMR ($CDCl_3$) δ 8.09 (d, 2H, J = 7.8 Hz), 7.49-7.37 (m, 4H), 7.26-7.19 (m, 2H), 5.91 (s, 1H), 5.30 (d, 1H, J = 9.0 Hz), 4.54 and 4.48 (AB quart, 2H, J = 13.8 Hz), 4.34 (t, 2H, J = 7.2 Hz), 4.30 (dt, 1H, J = 9.0, 3.3 Hz), 3.90 (dd, 1H, J = 9.3, 3.6 Hz), 3.75 (dd, 1H, J = 9.3, 3.3 Hz), 3.73 (s, 3H), 2.99 (s, 3H), 2.65 (t, 2H, J = 7.5 Hz), 2.00-1.89 (m, 2H), 1.78-1.68 (m, 2H).

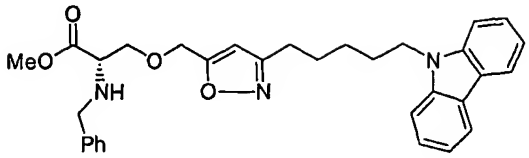
^{13}C NMR ($CDCl_3$) δ 170.10, 167.71, 163.29, 140.27, 125.62, 122.77, 120.33, 118.81, 108.56, 102.87, 71.51, 63.89, 56.13, 52.99, 42.46, 41.85, 28.29, 25.66, 25.60.

Example 13

General procedure

To a solution of amine (0.14 mmol) in 1.5 mL of 1,2-dichloroethane at 0 °C were added 4 Å powdered molecular sieves (40 mg). Aldehyde (0.17 mmol, 1.2 equiv.) was added, followed by sodium triacetoxyborohydride (35 mg, 0.17 mmol, 1.2 equiv.). After 5 min, the solution was warmed to room temperature, and the reaction was stirred for 12 h. Aqueous 3 N HCl (0.1 mL) was added and after 30 min the mixture was partitioned between EtOAc and saturated $NaHCO_3$ solution. The aqueous phase was re-extracted with EtOAc, and the combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography with hexane-EtOAc (2:1).

R = $PhCH_2$:

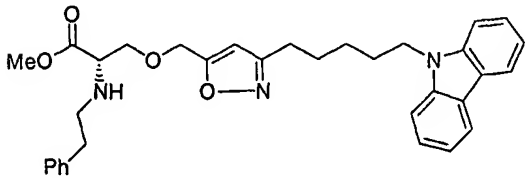


Yield, 78%; syrup; $[\alpha]_D$ +1.5 (c 1.3, $CHCl_3$).

^1H NMR ($CDCl_3$) δ 8.09 (d, 2H, J = 7.5 Hz), 7.49-7.19 (m, 11H), 5.95 (s, 1H), 4.53 (s, 2H), 4.30 (t, 2H, J = 7.2 Hz), 3.89 (d, 1H, J = 13.2 Hz), 3.76 (dd, 1H, J = 9.3, 4.8 Hz), 3.72 (s, 3H), 3.71 (dd, 1H, J = 9.3, 4.8 Hz), 3.65 (d, 1H, J = 13.2 Hz), 3.48 (t, 1H, J = 4.8 Hz), 2.60 (t, 2H, J = 7.5 Hz), 2.17 (br s, 1H), 1.96-1.85 (m, 2H), 1.73-1.62 (m, 2H), 1.49-1.38 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 173.18, 168.50, 163.53, 140.31, 139.44, 128.40, 128.24, 127.15, 125.59, 122.77, 120.32, 118.74, 108.56, 102.57, 71.90, 64.13, 60.26, 52.04, 52.00, 42.78, 28.59, 27.92, 26.77, 25.81.

R = $PhCH_2CH_2$:

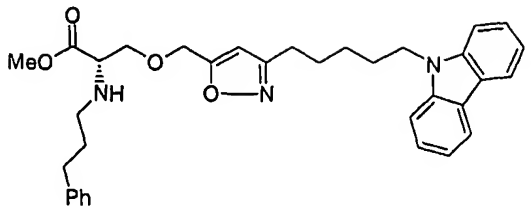


Yield, 69%; syrup; $[\alpha]_D$ –5.3 (c 2.0, $CHCl_3$).

^1H NMR ($CDCl_3$) δ 8.10 (d, 2H, J = 7.8 Hz), 7.49-7.37 (m, 4H), 7.30-7.15 (m, 7H), 5.93 (s, 1H), 4.52 (s, 2H), 4.31 (t, 2H, J = 7.2 Hz), 3.72 (dd, 1H, J = 9.3, 5.1 Hz), 3.71 (s, 3H), 3.68 (dd, 1H, J = 9.3, 5.1 Hz), 3.48 (t, 1H, J = 5.1 Hz), 3.00-2.70 (m, 4H), 2.60 (t, 1H, J = 7.5 Hz), 1.97-1.86 (m, 2H), 1.78 (br s, 1H), 1.73-1.62 (m, 2H), 1.50-1.39 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 173.06, 168.45, 163.52, 140.31, 139.55, 128.63, 128.40, 126.18, 125.59, 122.77, 120.32, 118.75, 108.56, 102.58, 71.60, 64.11, 61.31, 52.03, 49.52, 42.79, 36.50, 28.59, 27.92, 26.79, 25.82.

R = $PhCH_2CH_2CH_2$:



Yield, 66%; syrup; $[\alpha]_D$ –1.9 (c 2.4, $CHCl_3$).

^1H NMR ($CDCl_3$) δ 8.09 (d, 2H, J = 7.8 Hz), 7.49-7.36 (m, 4H), 7.29-7.12 (m, 7H), 5.96 (s, 1H), 4.54 (s, 2H), 4.29 (t, 2H, J = 7.2 Hz), 3.73 (dd, 1H, J = 9.3, 4.8 Hz), 3.71 (s, 3H), 3.68 (dd, 1H, J = 9.3, 4.8 Hz), 3.43 (t, 1H, J = 4.8 Hz), 2.73-2.46 (m, 6H), 1.95-1.61 (m, 7H), 1.49-1.38 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 173.28, 168.46, 163.51, 141.87, 140.29, 128.32, 128.27, 125.74, 125.58, 122.75, 120.31, 118.74, 108.56, 102.59, 71.75, 64.11, 61.28, 52.00, 47.68, 42.76, 33.34, 31.65, 28.57, 27.90, 26.76, 25.80.

Example 14

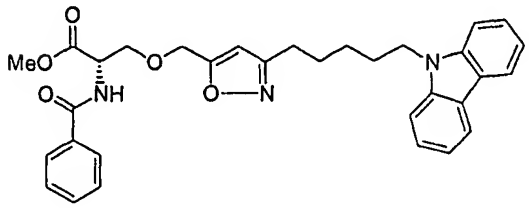
General procedure

Method A: To a solution of amine (0.10 mmol) in 2 mL of dichloromethane and 0.1 mL of Et_3N was added acyl chloride (0.15 mmol). The reaction mixture was stirred at room temperature 24 h, and then diluted with EtOAc (50 mL). The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography with hexane-EtOAc (2:1).

Method B: To a stirred solution of amine (0.1 mmol) in DMF (1 mL) at 0 °C was added EDC (40 mg, 0.2 mmol), HOBt (0.5 M in DMF, 0.4 mL, 0.2 mmol), the carboxylic acid (0.2 mmol), and triethylamine (52 μL, 0.3 mmol). The reaction mixture was stirred at room

temperature for 48 h, and then diluted with EtOAc (50 mL). The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography with hexane-EtOAc (2:1).

R = Ph:

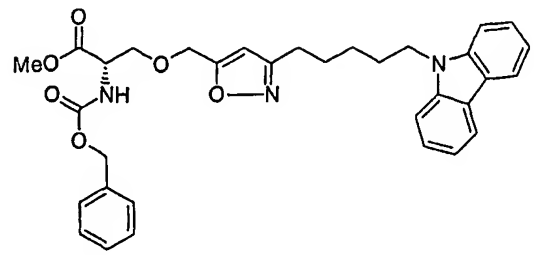


Method A: Yield, 71%; syrup; $[\alpha]_D$ +30 (c 1.2, $CHCl_3$).

^1H NMR ($CDCl_3$) δ 8.10 (d, 2H, J = 7.8 Hz), 7.84-7.50 (m, 2H), 7.52-7.36 (m, 7H), 7.26-7.19 (m, 2H), 6.98 (d, 1H, J = 7.8 Hz), 5.92 (s, 1H), 4.97 (dt, 1H, J = 7.8, 3.0 Hz), 4.55 (s, 2H), 4.29 (t, 2H, J = 7.2 Hz), 4.04 (dd, 1H, J = 9.3, 3.0 Hz), 3.86 (dd, 1H, J = 9.3, 3.0 Hz), 3.78 (s, 3H), 2.56 (t, 2H, J = 7.5 Hz), 1.95-1.84 (m, 2H), 1.69-1.58 (m, 2H), 1.47-1.37 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 170.41, 167.87, 166.99, 163.52, 140.30, 133.54, 131.88, 128.59, 127.11, 125.58, 122.75, 120.32, 118.76, 108.56, 102.86, 70.51, 63.97, 52.92, 52.79, 42.75, 28.55, 27.85, 26.74, 25.74.

R = $PhCH_2OCO$-:



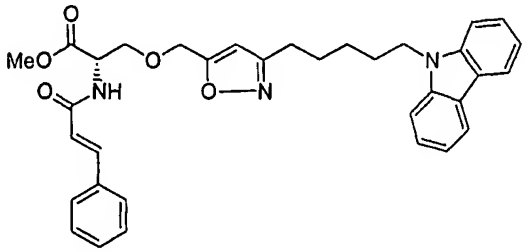
Method A: Yield, 58%; syrup; $[\alpha]_D$ +17 (c 1.32, $CHCl_3$).

^1H NMR ($CDCl_3$) δ 8.10 (d, 2H, J = 7.5 Hz), 7.49-7.19 (m, 11H), 5.92 (s, 1H), 5.60 (d, 1H, J = 8.7 Hz), 5.12 (s, 2H), 4.57-4.46 (m, 3H), 4.31 (t, 2H, J = 7.2 Hz), 3.94 (dd, 1H, J = 9.3,

3.0 Hz), 3.78-3.65 (m, 4H), 2.59 (t, 2H, J = 7.5 Hz), 1.97-1.86 (m, 2H), 1.72-1.61 (m, 2H), 1.49-1.38 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 170.35, 167.93, 163.54, 155.90, 140.32, 136.07, 128.52, 128.21, 128.08, 125.60, 122.77, 120.33, 118.76, 108.57, 102.77, 70.67, 67.12, 64.05, 54.22, 52.70, 42.78, 28.59, 27.90, 26.77, 25.80.

R = *trans*-PhCH=CHCO-:

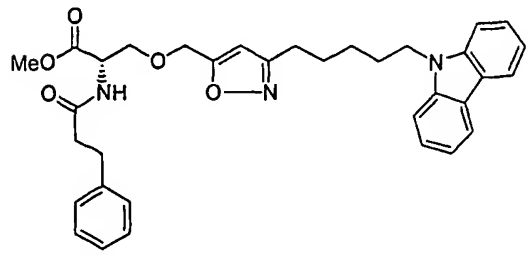


Method B: Yield, 83%; syrup.

^{1}H NMR ($CDCl_3$) δ 8.09 (d, 2H, J = 7.8 Hz), 7.64 (d, 1H, J = 15.6 Hz), 7.53-7.19 (m, 11H), 6.60 (d, 1H, J = 8.1 Hz), 6.46 (d, 1H, J = 15.6 Hz), 5.92 (s, 1H), 4.91 (dt, 1H, J = 8.1, 3.0 Hz), 4.52 (s, 2H), 4.26 (t, 2H, J = 7.2 Hz), 3.99 (dd, 1H, J = 9.3, 3.0 Hz), 3.80 (dd, 1H, J = 9.3, 3.0 Hz), 3.75 (s, 3H), 2.55 (t, 2H, J = 7.5 Hz), 1.91-1.80 (m, 2H), 1.68-1.57 (m, 2H), 1.44-1.32 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 170.33, 167.79, 165.47, 163.49, 142.25, 141.86, 134.47, 129.80, 128.73, 127.81, 125.54, 122.71, 120.27, 119.81, 118.71, 108.53, 102.89, 70.51, 63.91, 52.69, 52.59, 42.68, 28.48, 27.79, 26.68, 25.70.

R = $PhCH_2CH_2CO$-:

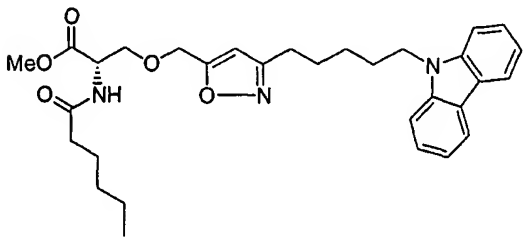


Method A: Yield, 77%; syrup; $[\alpha]_D$ +16 (c 2.4, $CHCl_3$).

^1H NMR ($CDCl_3$) δ 8.09 (d, 2H, J = 7.8 Hz), 7.48-7.36 (m, 4H), 7.29-7.13 (m, 7H), 6.24 (d, 1H, J = 7.8 Hz), 5.89 (s, 1H), 4.75 (dt, 1H, J = 8.1, 3.0 Hz), 4.46 and 4.41 (AB quart, 2H, J = 13.8 Hz), 4.29 (t, 2H, J = 7.2 Hz), 3.89 (dd, 1H, J = 9.3, 3.0 Hz), 3.71 (s, 3H), 3.63 (dd, 1H, J = 9.3, 3.0 Hz), 2.96 (t, 2H, J = 7.8 Hz), 2.63-2.48 (m, 4H), 1.96-1.85 (m, 2H), 1.71-1.60 (m, 2H), 1.48-1.37 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 171.84, 170.29, 167.80, 163.48, 140.53, 140.28, 128.44, 128.28, 126.18, 125.57, 122.74, 120.31, 118.74, 108.54, 102.85, 70.49, 63.89, 52.63, 52.30, 42.73, 37.94, 31.32, 28.55, 27.88, 26.74, 25.76.

R = $CH_3CH_2CH_2CH_2CH_2$-:

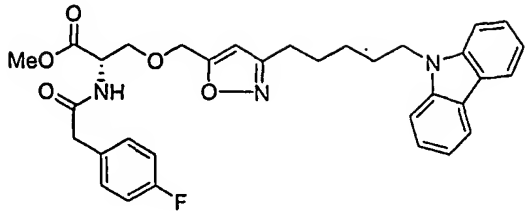


Method A: yield, 82%; syrup; $[\alpha]_D$ +28.1 (c 1.92, $CHCl_3$).

^1H NMR ($CDCl_3$) δ 8.10 (d, 2H, J = 7.8 Hz), 7.49-7.37 (m, 4H), 7.26-7.18 (m, 2H), 6.28 (d, 1H, J = 8.1 Hz), 5.91 (s, 1H), 4.77 (dt, 1H, J = 8.1, 3.0 Hz), 4.54 and 4.48 (AB quart, 2H, J = 14.1 Hz), 4.31 (t, 2H, J = 7.2 Hz), 3.92 (dd, 1H, J = 9.3, 3.0 Hz), 3.74 (s, 3H), 3.72 (dd, 1H, J = 9.3, 3.0 Hz), 2.60 (t, 2H, J = 7.5 Hz), 2.26-2.20 (m, 2H), 1.97-1.86 (m, 2H), 1.73-1.57 (m, 4H), 1.49-1.23 (m, 6H), 0.92-0.84 (m, 3H).

^{13}C NMR ($CDCl_3$) δ 172.99, 170.45, 167.81, 163.48, 140.28, 125.56, 122.75, 120.30, 118.74, 108.54, 102.87, 70.53, 63.89, 52.63, 52.25, 42.74, 36.38, 31.28, 28.55, 27.88, 26.74, 25.76, 25.12, 22.31, 13.88.

R = 4-F-$PhCH_2$-:

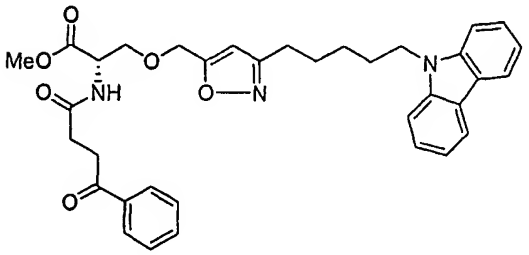


Method B: Yield, 73%; syrup; $[\alpha]_D$ +16.2 (c 2.2, $CHCl_3$).

^1H NMR ($CDCl_3$) δ 8.09 (d, 2H, J = 7.8 Hz), 7.49-7.36 (m, 4H), 7.28-7.18 (m, 4H), 7.06-6.96 (m, 2H), 6.30 (d, 1H, J = 8.1 Hz), 5.84 (s, 1H), 4.73 (dt, 1H, J = 8.4, 3.0 Hz), 4.45 (s, 2H), 4.31 (t, 2H, J = 7.2 Hz), 3.89 (dd, 1H, J = 9.3, 3.0 Hz), 3.71 (s, 3H), 3.68 (dd, 1H, J = 9.3, 3.3 Hz), 3.56 (s, 2H), 2.60 (t, 2H, J = 7.5 Hz), 1.97-1.86 (m, 2H), 1.72-1.61 (m, 2H), 1.49-1.40 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 170.51, 170.15, 167.69, 163.66 and 160.39, 163.49, 140.29, 130.93 and 130.83, 130.13 and 130.09, 125.58, 122.75, 120.31, 118.75, 115.84 and 115.56, 108.55, 102.87, 70.17, 63.81, 52.69, 52.49, 42.74, 42.44, 28.56, 27.89, 26.75, 25.76.

R = $PhCOCH_2CH_2$-:



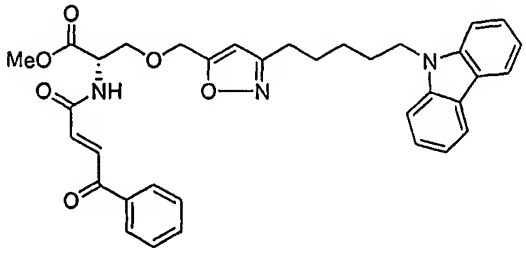
Method B: Yield, 70%; syrup; $[\alpha]_D$ +22.7 (c 2.1, $CHCl_3$).

^1H NMR ($CDCl_3$) δ 8.09 (d, 2H, J = 7.8 Hz), 7.98-7.92 (m, 2H), 7.56-7.36 (m, 7H), 7.26-7.19 (m, 2H), 6.58 (d, 1H, J = 8.1 Hz), 5.97 (s, 1H), 4.76 (dt, 1H, J = 8.1, 3.0 Hz), 4.57 and 4.51 (AB quart, 2H, J = 14.1 Hz), 4.29 (t, 2H, J = 7.2 Hz), 3.93 (dd, 1H, J = 9.3, 3.0 Hz), 3.74 (dd, 1H, J = 9.3, 3.3 Hz), 3.73 (s, 3H), 3.45-3.23 (m, 2H), 2.70 (t, 2H, J = 6.6 Hz), 2.59 (t, 2H, J = 7.5 Hz), 1.95-1.85 (m, 2H), 1.74-1.61 (m, 2H), 1.49-1.38 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 198.57, 171.90, 170.31, 167.96, 163.53, 140.27, 136.45, 133.17,

128.53, 127.97, 125.56, 122.73, 120.29, 118.72, 108.54, 102.80, 70.45, 64.04, 52.63, 52.51, 42.74, 33.66, 29.90, 28.55, 27.87, 26.75, 25.77.

R = $PhCOCH_2=CH_2$-:

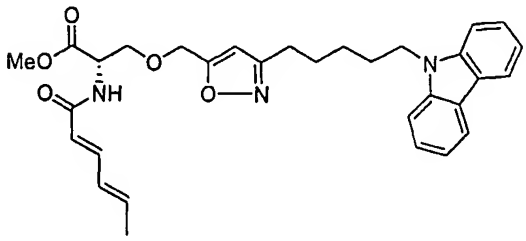


Method B: Yield, 61%; syrup; $[\alpha]_D$ +22.1 (c 1.03, $CHCl_3$).

^1H NMR ($CDCl_3$) δ 8.12-7.99 (m, 4H), 7.96 (d, 1H, J = 15.3 Hz), 7.63-7.36 (m, 7H), 7.26-7.19 (m, 2H), 7.03 (d, 1H, J = 15.3 Hz), 6.84 (d, 1H, J = 8.1 Hz), 5.93 (s, 1H), 4.89 (dt, 1H, J = 8.1, 3.0 Hz), 4.55 and 4.50 (AB quart, 2H, J = 13.8 Hz), 4.30 (t, 2H, J = 7.2 Hz), 4.01 (dd, 1H, J = 9.3, 3.0 Hz), 3.81 (dd, 1H, J = 9.3, 3.0 Hz), 3.77 (s, 3H), 2.59 (t, 2H, J = 7.5 Hz), 1.96-1.85 (m, 2H), 1.72-1.60 (m, 2H), 1.48-1.37 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 189.49, 169.85, 167.72, 163.75, 163.57, 140.31, 136.68, 134.34, 134.04, 133.78, 128.84, 128.83, 125.60, 122.76, 120.32, 118.76, 108.57, 102.96, 70.24, 63.96, 52.89, 52.84, 42.77, 28.57, 27.88, 26.77, 25.78.

R = *trans,trans*-MeCH=CHCH=CH-:



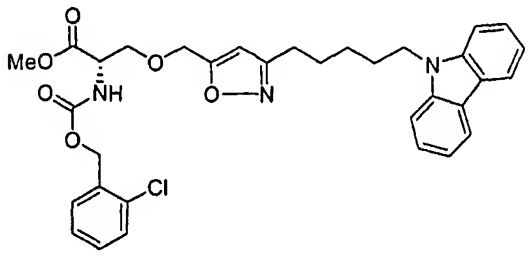
Method B: Yield, 81%; syrup; $[\alpha]_D$ +30 (c 1.7, $CHCl_3$).

^1H NMR ($CDCl_3$) δ 8.10 (d, 2H, J = 7.8 Hz), 7.49-7.15 (m, 7H), 6.31 (d, 1H, J = 8.1 Hz), 6.20-6.01 (m, 2H), 5.91 (s, 1H), 5.77 (d, 1H, J = 15.0 Hz), 4.85 (dt, 1H, J = 8.1, 3.0 Hz),

4.52 (s, 2H), 4.31 (t, 2H, J = 7.2 Hz), 3.96 (dd, 1H, J = 9.3, 3.0 Hz), 3.76 (dd, 1H, J = 9.3, 3.0 Hz), 3.75 (s, 3H), 2.59 (t, 2H, J = 7.5 Hz), 1.96-1.86 (m, 2H), 1.81 (d, 3H, J = 5.1 Hz), 1.72-1.61 (m, 2H), 1.49-1.38 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 170.45, 167.87, 165.93, 163.51, 142.23, 140.30, 138.59, 129.52, 125.59, 122.76, 120.57, 120.33, 118.76, 108.56, 102.85, 70.60, 63.98, 52.69, 52.49, 42.76, 28.56, 27.86, 26.74, 25.76, 18.56.

R = *o*-Cl-PhCH_2O-:

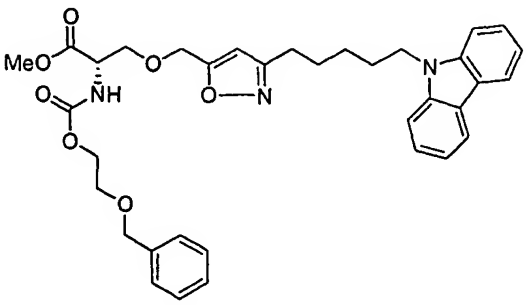


Method A: Yield, 79%; syrup; $[\alpha]_D$ +10.8 (c 2.6, $CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 8.09 (d, 2H, J = 7.5 Hz), 7.49-7.19 (m, 10H), 5.92 (s, 1H), 5.66 (d, 1H, J = 8.7 Hz), 5.24 (s, 2H), 4.57-4.46 (m, 3H), 4.30 (t, 2H, J = 7.2 Hz), 3.94 (dd, 1H, J = 9.3, 3.3 Hz), 3.76 (dd, 1H, J = 9.3, 3.3 Hz), 3.74 (s, 3H), 2.59 (t, 2H, J = 7.5 Hz), 1.96-1.85 (m, 2H), 1.72-1.61 (m, 2H), 1.49-1.37 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 170.28, 167.88, 163.52, 155.65, 140.29, 133.84, 129.50, 129.45, 129.36, 126.84, 125.58, 122.75, 120.31, 118.74, 108.56, 102.78, 70.58, 64.29, 64.02, 54.25, 52.70, 42.76, 28.56, 27.89, 26.76, 25.78.

R = PhCH_2OCH_2CH_2O-:

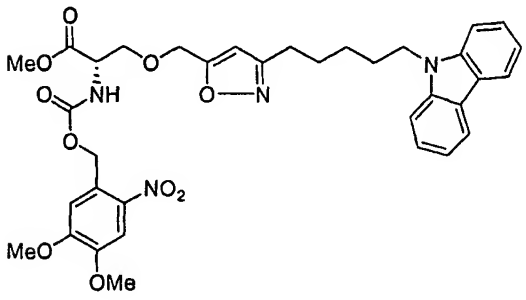


Method A: Yield, 76%; syrup; $[\alpha]_D$ +11 (c 2.5, $CHCl_3$).

^1H NMR ($CDCl_3$) δ 8.10 (d, 2H, J = 7.8 Hz), 7.49-7.19 (m, 11H), 5.93 (s, 1H), 5.62 (d, 1H, J = 8.4 Hz), 4.57-4.44 (m, 5H), 4.33-4.22 (s, 4H), 3.93 (dd, 1H, J = 9.3, 3.3 Hz), 3.76-3.61 (m, 6H), 2.60 (t, 2H, J = 7.5 Hz), 1.97-1.86 (m, 2H), 1.73-1.62 (m, 2H), 1.49-1.37 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 170.31, 167.94, 163.52, 155.87, 140.30, 137.77, 128.39, 127.73, 125.59, 122.75, 120.32, 118.74, 108.56, 102.75, 73.14, 70.68, 68.15, 64.46, 64.05, 54.15, 52.67, 42.76, 28.57, 27.90, 26.76, 25.78.

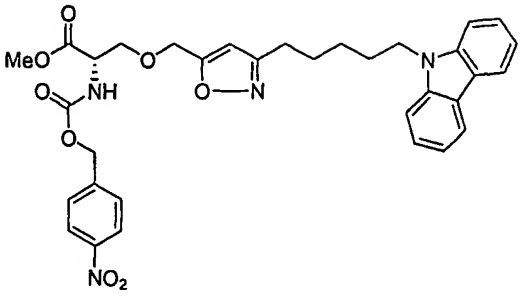
R = 2-NO_2-4,5-di-MeO-$PhCH_2O$-:



Method A: Yield, 71%.

^1H NMR ($CDCl_3$) δ 8.09 (d, 2H, J = 8.1 Hz), 7.69 (s, 1H), 7.48-7.36 (m, 4H), 7.26-7.19 (m, 2H), 7.03 (s, 1H), 5.93 (s, 1H), 5.76 (d, 1H, J = 8.7 Hz), 5.62 and 5.46 (AB quart, 2H, J = 15.3 Hz), 4.60-4.45 (m, 3H), 4.30 (t, 2H, J = 7.2 Hz), 4.00-3.90 (m, 7H), 3.77 (dd, 1H, J = 9.6, 3.3 Hz), 3.74 (s, 3H), 2.59 (t, 2H, J = 7.5 Hz), 1.97-1.86 (m, 2H), 1.73-1.61 (m, 2H), 1.49-1.38 (m, 2H).

R = *p*-NO_2-$PhCH_2O$-:

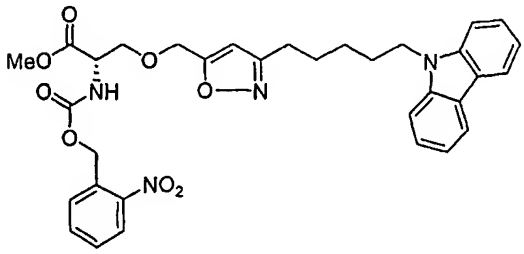


Method A: Yield, 81%; $[\alpha]_D$ +8.7 (c 2.8, $CHCl_3$).

^1H NMR ($CDCl_3$) δ 8.23-8.06 (m, 4H), 7.50-7.36 (m, 6H), 7.26-7.19 (m, 2H), 5.92 (s, 1H), 5.70 (d, 1H, *J* = 8.4 Hz), 5.22 and 5.17 (AB quart, 2H, *J* = 13.5 Hz), 4.52 (s, 2H), 4.50 (m, 1H), 4.30 (t, 2H, *J* = 7.2 Hz), 3.94 (dd, 1H, *J* = 9.3, 3.0 Hz), 3.76 (dd, 1H, *J* = 9.3, 3.0 Hz), 3.75 (s, 3H), 2.60 (t, 2H, *J* = 7.5 Hz), 1.96-1.86 (m, 2H), 1.72-1.61 (m, 2H), 1.49-1.38 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 170.15, 167.69, 163.52, 155.43, 147.54, 143.55, 140.28, 127.97, 125.57, 123.70, 122.74, 120.31, 118.75, 108.54, 102.93, 70.41, 65.46, 63.92, 54.25, 52.77, 42.73, 28.55, 27.89, 26.74, 25.76.

R = *o*-NO_2-$PhCH_2O$-:

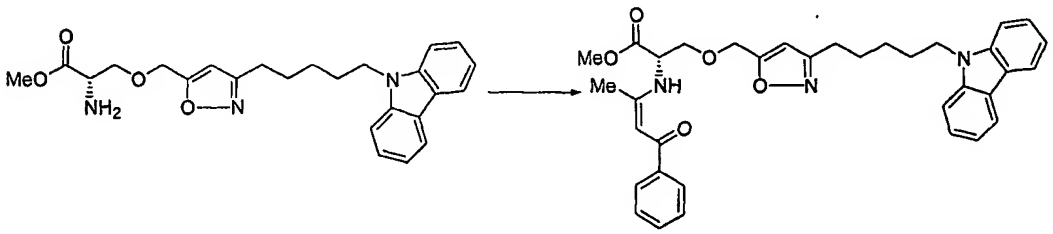


To a stirred solution of 2-nitrophenyl chloroformate (201 mg, 1 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added 2-nitrobenzyl alcohol (153 mg, 1 mmol), followed by *i*-$PrNEt_2$ (300 μL) and DMAP (5 mg). The reaction mixture was slowly warmed to room temperature and stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated aqueous $NaHCO_3$ until the water phase is colorless, and brine.

The organic layer was dried (Na_2SO_4), and concentrated. The residue was purified by chromatography with hexane-EtOAc (5:1) to provide the corresponding carbonate as a white solid. ^1H NMR ($CDCl_3$) δ 8.33-8.28 (m, 2H), 8.20 (d, 1H, J = 8.1 Hz), 7.78-7.68 (m, 2H), 7.63-7.55 (m, 1H), 7.45-7.40 (m, 2H), 5.74 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 155.30, 152.09, 134.13, 130.58, 129.51, 129.08, 125.40, 125.37, 121.71, 67.36.

To a stirred solution of the amine (30 mg) and the above carbonate (20 mg) in CH_2Cl_2 (2 mL) was added Et_3N (100 μL). The reaction mixture was stirred at room temperature for 5 days. After that the mixture was diluted with EtOAc, washed with saturate aq. $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography with hexane-EtOAc (1:1) to provide the corresponding carbamate. Yield, 71%; $[\alpha]_D$ +24 (c 0.91, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 8.14-8.04 (m, 3H), 7.68-7.18 (m, 9H), 5.95 (s, 1H), 5.73 (d, 1H, J = 8.7 Hz), 5.58 and 5.52 (AB quart, 2H, J = 15.0 Hz), 4.59-4.47 (m, 3H), 4.32 (t, 2H, J = 7.2 Hz), 3.95 (dd, 1H, J = 9.3, 3.0 Hz), 3.78 (dd, 1H, J = 9.3, 3.0 Hz), 3.76 (s, 3H), 2.61 (t, 2H, J = 7.5 Hz), 1.98-1.87 (m, 2H), 1.74-1.63 (m, 2H), 1.51-1.39 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 171.16, 170.22, 167.80, 163.57, 155.37, 140.31, 133.83, 132.88, 128.52, 125.60, 124.97, 122.77, 120.33, 118.77, 108.57, 102.92, 70.47, 64.01, 63.67, 54.28, 52.79, 42.78, 28.59, 27.92, 26.78, 25.81.

R = PhCOCH=C(Me)-:



A mixture of the amine (85 mg, 0.2 mmol), CH_2Cl_2 (2 mL), Et_3N (42 μL, 0.3 mmol), anhydrous MgSO4 (300 mg), and 1-benzoylacetone (98 mg, 0.6 mmol) was stirred at room temperature for 5 days. After that the reaction mixture was filtered though Celite, and the filtrate was concentrated in vacuo. The residue was purified by chromatography with hexanes/EtOAc (2:1) to give the desired product as a syrup (80 mg, 72%).

$[\alpha]_D$ +16.5 (c 0.8, $CHCl_3$).

^1H NMR ($CDCl_3$) δ 8.09 (d, 2H, J = 7.8 Hz), 7.90-7.83 (m, 2H), 7.49-7.18 (m, 9H), 6.17 (s,

1H), 5.76 (s, 1H), 4.62 (s, 2H), 4.42-4.35 (m, 1H), 4.26 (t, 2H, J = 7.2 Hz), 3.92 (dd, 1H, J = 9.3, 5.1 Hz), 3.85 (dd, 1H, J = 9.3, 4.2 Hz), 3.77 (s, 3H), 2.58 (t, 2H, J = 7.5 Hz), 2.02 (s, 3H), 1.90-1.79 (m, 2H), 1.70-1.59 (m, 2H), 1.45-1.34 (m, 2H).

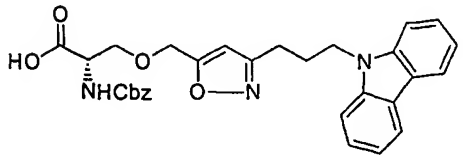
^{13}C NMR ($CDCl_3$) δ 188.73, 169.77, 168.19, 163.82, 163.10, 140.30, 139.91, 130.79, 128.14, 127.02, 125.58, 122.75, 120.29, 118.72, 108.59, 102.83, 93.60, 71.15, 64.46, 56.35, 52.92, 42.78, 28.55, 27.83, 26.79, 25.83, 19.57.

Example 15

General procedure

To a stirred solution of methyl ester (0.1 mmol) in THF (2 mL) and water (2 mL) at 0 °C was added slowly a 2 N aqueous LiOH solution (0.1 mL, 0.2 mmol). The reaction mixture was minored by TLC. After completion the reaction mixture was neutralized with 0.5 N $NaHSO_4$ to pH 4, and diluted with EtOAc (100 mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography to give the acid.

n = 1, R = Cbz:



Yield, 51%; $[\alpha]_D$ +9.6 (c 1.0, $CHCl_3$).

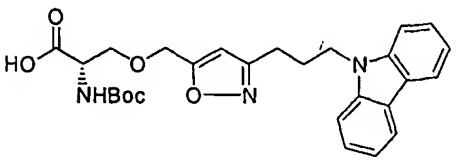
^{1}H NMR ($CDCl_3$) δ 8.02 (d, 2H, J = 7.5 Hz), 7.38-7.00 (m, 11H), 6.11 (br s, 1H), 5.67 (s, 1H), 4.97 (d, 1H, J = 12.0 Hz), 4.82 (d, 1H, J = 12.0 Hz), 4.40-4.10 (m, 5H), 4.00-3.20 (m, 3H), 2.41 (t, 2H, J = 7.1 Hz), 2.10-1.90 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 175.75, 168.05, 162.82, 156.65, 140.22, 136.15, 128.35, 127.98,

127.90, 125.69, 122.77, 120.31, 118.93, 108.58, 103.04, 70.88, 66.79, 63.55, 55.37, 41.99, 26.78, 23.60.

Anal. Calcd for $C_{30}H_{29}N_3O_6$: C, 68.30; H, 5.54; N, 7.96. Found: C, H, N.

n = 1, R = Boc:



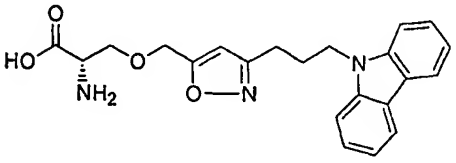
Yield, 81%; $[\alpha]_D$ +25 (c 0.8, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.08 (d, 2H, J = 7.8 Hz), 7.48-7.39 (m, 4H), 7.24-7.18 (m, 2H), 6.10 (s, 1H), 4.56 (s, 2H), 4.43 (t, 2H, J = 6.9 Hz), 4.17 (m, 1H), 3.89 (dd, 1H, J = 9.3, 3.9 Hz), 3.77 (dd, 1H, J = 9.3, 3.3 Hz), 2.68 (t, 2H, J = 7.5 Hz), 2.31-2.20 (m, 2H), 1.40 (s, 9H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 176.41, 169.53, 163.66, 156.81, 140.85, 126.19, 123.37, 120.67, 119.41, 109.11, 103.40, 80.17, 72.09, 64.28, 55.76, 42.48, 28.51, 27.53, 24.17.

Anal. Calcd for $C_{27}H_{31}N_3O_6$: C, 65.71; H, 6.33; N, 8.51. Found: C, H, N.

n = 1, R = H:



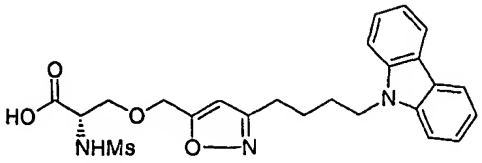
Yield, 79%; $[\alpha]_D$ +60.4 (c 0.28, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.09 (d, 2H, J = 7.5 Hz), 7.50-7.38 (m, 4H), 7.28-7.16 (m, 2H), 6.20 (s, 1H), 4.47 (t, 2H, J = 6.6 Hz), 4.24 (m, 1H), 4.16 (s, 2H), 4.04-3.56 (m, 2H), 2.73 (m, 2H), 2.30 (m, 2H).

^{13}C NMR (DMSO-d_6) δ 168.81, 162.98, 139.94, 125.79, 122.08, 120.32, 118.81, 109.24, 103.36, 62.89, 41.65, 26.92, 23.03.

Anal. Calcd for $C_{22}H_{23}N_3O_4$: C, 67.16; H, 5.89; N, 10.68. Found: C, H, N.

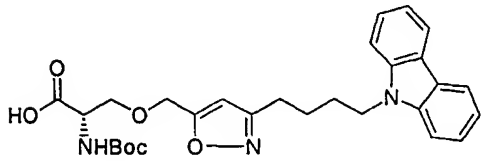
n = 2, R = $MeSO_2$:



Yield, 11%.

^{1}H NMR ($CDCl_3$) δ 7.99 (d, 2H, J = 7.5 Hz), 7.38-7.08 (m, 6H), 6.57 (br s, 1H), 5.81 (s, 1H), 4.45 (br s, 2H), 4.26-4.00 (m, 3H), 3.74 (br s, 2H), 2.85 (s, 3H), 2.55-2.00 (m, 3H), 1.75-1.65 (m, 2H), 1.60-1.40 (m, 2H).

n = 2, R = Boc:



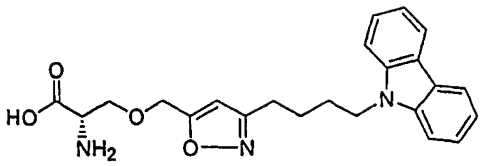
Yield, 57%; $[\alpha]_D$ +16.6 (c 0.72, $CHCl_3$).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.08 (d, 2H, J = 7.8 Hz), 7.48-7.39 (m, 4H), 7.24-7.18 (m, 2H), 6.02 (s, 1H), 4.53 (s, 2H), 4.36 (t, 2H, J = 6.9 Hz), 4.17 (m, 1H), 3.89 (dd, 1H, J = 9.6, 4.2 Hz), 3.77 (dd, 1H, J = 9.6, 3.3 Hz), 2.63 (t, 2H, J = 7.5 Hz), 1.99-1.88 (m, 2H), 1.76-1.64 (m, 2H), 1.43 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 176.87, 168.30, 163.23, 156.16, 140.26, 125.63, 122.75, 120.32, 118.82, 108.58, 102.97, 80.15, 71.00, 63.69, 54.98, 42.42, 28.36, 28.28, 25.57.

Anal. Calcd for $C_{28}H_{33}N_3O_6$: C, 66.26; H, 6.55; N, 8.28. Found: C, H, N.

n = 2, R = H:



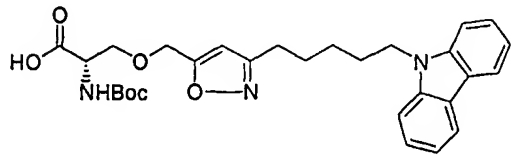
Yield, 72%; $[\alpha]_D$ +45 (c 0.28, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.08 (d, 2H, J = 7.8 Hz), 7.50-7.38 (m, 4H), 7.24-7.18 (m, 2H), 6.12 (s, 1H), 4.59 (s, 2H), 4.38 (t, 2H, J = 6.9 Hz), 4.00-3.65 (m, 3H), 2.65 (t, 2H, J = 7.5 Hz), 2.00-1.89 (m, 2H), 1.77-1.66 (m, 2H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 170.62, 168.86, 164.28, 140.93, 126.16, 123.35, 120.69, 119.32, 109.18, 103.72, 69.81, 64.14, 55.31, 42.84, 28.83, 26.13, 26.05.

Anal. Calcd for $C_{23}H_{25}N_3O_4$: C, 67.80; H, 6.18; N, 10.31. Found: C, H, N.

n = 3, R = Boc:



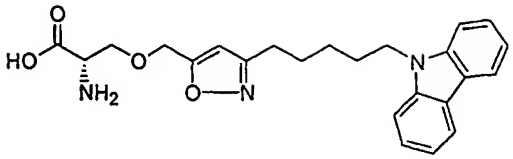
Yield, 65%; $[\alpha]_D$ +16.8 (c 1.2, $CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 8.06 (d, 2H, J = 7.8 Hz), 7.45-7.32 (m, 4H), 7.19 (t, 2H, J = 7.8 Hz), 5.92 (s, 1H), 5.73 (br s, 1H), 4.48 (s, 2H), 4.35-4.10 (m, 3H), 3.79 (m, 1H), 3.69 (m, 1H), 2.47 (t, 2H, J = 7.5 Hz), 1.87-1.76 (m, 2H), 1.61-1.50 (m, 2H), 1.40-1.26 (m, 2H), 1.33 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 175.80, 168.09, 163.54, 155.95, 140.29, 125.59, 122.74, 120.31, 118.75, 108.58, 102.99, 79.72, 71.18, 63.74, 54.84, 42.74, 28.56, 28.27, 27.84, 26.81, 25.76.

Anal. Calcd for $C_{29}H_{35}N_3O_6$: C, 66.78; H, 6.76; N, 8.06. Found: C, H, N.

n = 3, R = H:



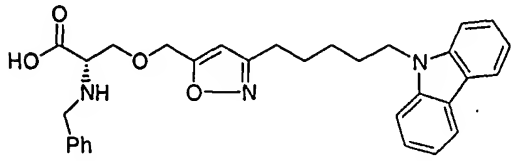
Yield, 83%; $[\alpha]_D$ +35 (c 0.5, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.09 (d, 2H, J = 7.8 Hz), 7.49-7.40 (m, 4H), 7.26-7.18 (m, 2H), 6.15 (s, 1H), 4.62 (s, 2H), 4.36 (t, 2H, J = 6.9 Hz), 3.95 (dd, 1H, J = 9.9, 3.3 Hz), 3.83 (dd, 1H, J = 9.9, 7.5 Hz), 3.73 (dd, 1H, J = 7.5, 3.3 Hz), 2.60 (t, 2H, J = 7.5 Hz), 1.99-1.88 (m, 2H), 1.73-1.62 (m, 2H), 1.49-1.38 (m, 2H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 170.45, 168.82, 164.62, 141.05, 126.19, 123.41, 120.72, 119.32, 109.26, 103.92, 69.85, 64.21, 55.42, 43.17, 29.12, 28.47, 27.26, 26.23.

Anal. Calcd for $C_{24}H_{27}N_3O_4$: C, 68.39; H, 6.46; N, 9.97. Found: C, H, N.

n = 3, R = $PhCH_2$:



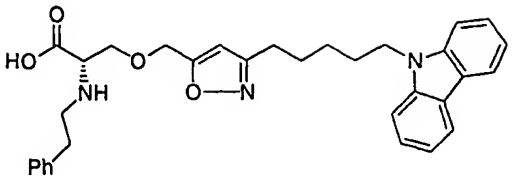
Yield, 86%; $[\alpha]_D$ +55 (c 0.44, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.09 (d, 2H, J = 7.8 Hz), 7.49-7.28 (m, 9H), 7.24-7.18 (m, 2H), 6.13 (s, 1H), 4.56 (s, 2H), 4.35 (t, 2H, J = 7.2 Hz), 4.05 (d, 1H, J = 12.3 Hz), 3.94 (d, 1H, J = 12.6 Hz), 3.85 (d, 2H, J = 3.6 Hz), 3.51 (m, 1H), 2.60 (t, 2H, J = 7.5 Hz), 1.98-1.87 (m, 2H), 1.73-1.62 (m, 2H), 1.49-1.38 (m, 2H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 169.11, 164.52, 140.97, 129.73, 129.34, 128.95, 126.13, 123.33, 120.67, 119.25, 109.20, 103.70, 70.96, 64.18, 62.26, 51.61, 43.14, 29.07, 28.41, 27.21, 26.19.

Anal. Calcd for $C_{31}H_{33}N_3O_4$: C, 72.78; H, 6.50; N, 8.21. Found: C, H, N.

n = 3, R = $PhCH_2CH_2$:



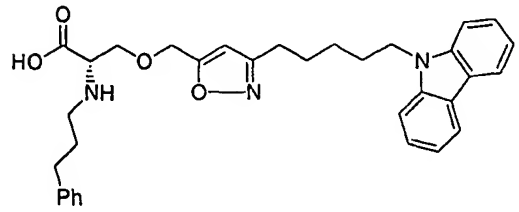
Yield, 91%; $[\alpha]_D$ +34.5 (c 0.33, MeOH-CH_2Cl_2 1:1).

^1H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.10 (d, 2H, J = 7.8 Hz), 7.49-7.15 (m, 11H), 6.09 (s, 1H), 4.62 and 4.56 (AB quart, 2H, J = 13.8 Hz), 4.35 (t, 2H, J = 6.9 Hz), 3.98 (dd, 1H, J = 10.8, 3.6 Hz), 3.90 (dd, 1H, J = 10.8, 6.6 Hz), 3.66 (dd, 1H, J = 6.6, 3.6 Hz), 3.25-3.17 (m, 2H), 3.03-2.96 (m, 2H), 2.60 (t, 2H, J = 7.5 Hz), 1.98-1.88 (m, 2H), 1.72-1.61 (m, 2H), 1.49-1.38 (m, 2H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 169.08, 168.08, 164.30, 140.72, 136.36, 129.26, 128.86, 127.60, 125.95, 123.10, 120.56, 119.09, 108.97, 103.83, 68.56, 63.92, 62.17, 48.20, 43.01, 32.71, 28.88, 28.20, 27.07, 26.03.

Anal. Calcd for $C_{32}H_{35}N_3O_4$: C, 73.12; H, 6.71; N, 7.99. Found: C, H, N.

n = 3, R = $PhCH_2CH_2CH_2$:



Yield, 83%; $[\alpha]_D$ +2.8 (c 1.6, MeOH-CH_2Cl_2 1:1).

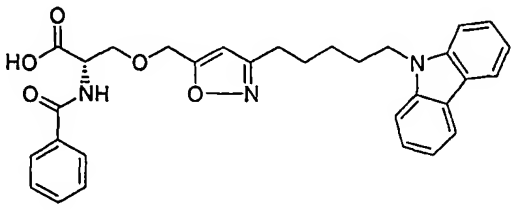
^1H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.09 (d, 2H, J = 7.8 Hz), 7.48-7.14 (m, 11H), 6.08 (s, 1H), 4.58 and 4.53 (AB quart, 2H, J = 13.8 Hz), 4.32 (t, 2H, J = 7.2 Hz), 3.93 (dd, 1H, J = 10.8, 3.6 Hz), 3.87 (dd, 1H, J = 10.8, 6.3 Hz), 3.61 (dd, 1H, J = 6.3, 3.6 Hz), 3.05-2.88 (m, 2H), 2.67 (t, 2H, J = 7.5 Hz), 2.57 (t, 2H, J = 7.5 Hz), 2.06-1.85 (m, 4H), 1.70-1.59 (m, 2H), 1.46-1.34 (m, 2H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 169.51, 168.40, 164.47, 140.89, 140.53, 129.04, 128.67,

126.84, 126.09, 123.26, 120.65, 119.23, 109.15, 103.93, 68.83, 64.05, 62.30, 46.86, 43.07, 33.01, 29.01, 28.34, 28.18, 27.16, 26.13.

Anal. Calcd for $C_{33}H_{37}N_3O_4$: C, 73.44; H, 6.91; N, 7.79. Found: C, H, N.

n = 3, R = PhCO-:

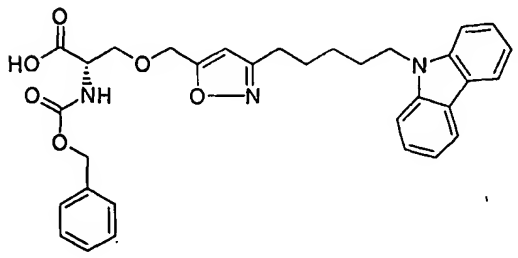


Yield, 79%; $[\alpha]_D$ +18.7 (c 1.1, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.07 (d, 2H, J = 7.8 Hz), 7.84-7.77 (m, 2H), 7.47-7.15 (m, 9H), 6.00 (s, 1H), 4.62 (m, 1H), 4.53 (s, 2H), 4.29 (t, 2H, J = 7.2 Hz), 4.05 (dd, 1H, J = 9.6, 4.2 Hz), 3.92 (dd, 1H, J = 9.6, 3.3 Hz), 2.48 (t, 2H, J = 7.5 Hz), 1.91-1.80 (m, 2H), 1.61-1.50 (m, 2H), 1.41-1.27 (m, 2H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 176.31, 169.30, 168.55, 164.35, 140.89, 134.35, 132.24, 128.97, 127.60, 126.09, 123.27, 120.65, 119.22, 109.16, 103.40, 71.73, 64.23, 55.62, 43.07, 29.00, 28.28, 27.15, 26.07.

n = 3, R = $PhCH_2OCO$-:

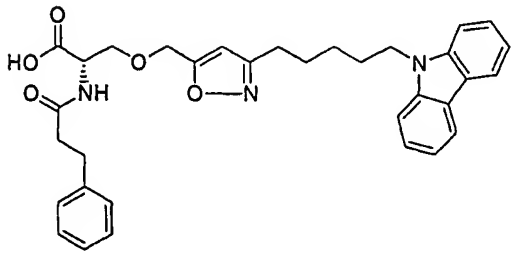


Yield, 86%; $[\alpha]_D$ +26.1 (c 0.85, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.12-8.05 (m, 2H), 7.49-7.15 (m, 11H), 6.08 (s, 1H), 5.14-5.02 (m, 2H), 4.56 (s, 2H), 4.33 (t, 2H, J = 7.2 Hz), 4.29 (m, 1H), 3.95-3.75 (m, 2H), 2.56 (t, 2H, J = 7.5 Hz), 1.96-1.85 (m, 2H), 1.70-1.59 (m, 2H), 1.46-1.35 (m, 2H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 174.74, 169.63, 164.47, 157.29, 140.99, 137.15, 128.92, 128.48, 128.27, 126.15, 123.35, 120.68, 119.27, 109.24, 103.37, 72.23, 67.15, 64.39, 56.37, 43.14, 29.08, 28.41, 27.20, 26.18.

n = 3, R = $PhCH_2CH_2CO$-:

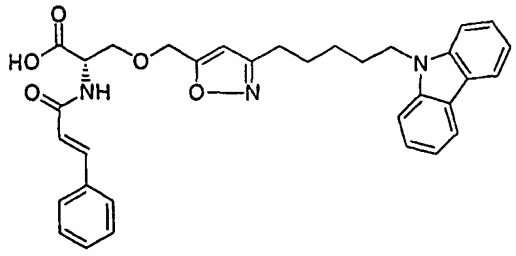


Yield, 93%; $[\alpha]_D$ +15.7 (c 1.5, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.07 (d, 2H, *J* = 7.8 Hz), 7.47-7.37 (m, 4H), 7.27-7.09 (m, 7H), 6.05 (s, 1H), 4.48 (br s, 3H), 4.30 (t, 2H, *J* = 6.9 Hz), 3.90 (dd, 1H, *J* = 9.3, 3.9 Hz), 3.73 (dd, 1H, *J* = 9.3, 2.4 Hz), 2.92 (t, 2H, *J* = 7.5 Hz), 2.65-2.45 (m, 4H), 1.93-1.82 (m, 2H), 1.69-1.58 (m, 2H), 1.45-1.33 (m, 2H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 174.89, 173.71, 169.52, 164.44, 141.34, 140.97, 128.91, 128.78, 126.62, 126.14, 123.34, 120.67, 119.27, 109.23, 103.42, 72.01, 64.30, 54.90, 43.11, 38.49, 32.15, 29.06, 28.41, 27.20, 26.17.

n = 3, R = *trans*-PhCH=CHCO-:



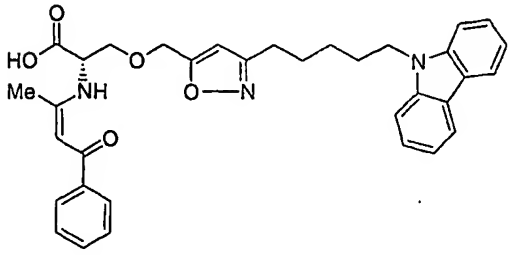
Yield, 92%; $[\alpha]_D$ +25 (c 1.72, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.07 (d, 2H, *J* = 7.8 Hz), 7.58-7.15 (m, 12H), 6.64 (d, 1H, *J* = 15.6 Hz), 6.09 (s, 1H), 4.63 (m, 1H), 4.58 (s, 2H), 4.27 (t, 2H, *J* = 7.2 Hz), 4.01 (m,

1H), 3.89 (m, 1H), 2.52 (t, 2H, J = 7.5 Hz), 1.89-1.78 (m, 2H), 1.65-1.54 (m, 2H), 1.40-1.28 (m, 2H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 174.77, 169.61, 167.13, 164.47, 141.42, 140.97, 135.41, 130.23, 129.30, 128.29, 126.13, 123.34, 121.27, 120.66, 119.26, 109.23, 103.40, 72.12, 64.34, 55.30, 43.10, 29.02, 28.35, 27.19, 26.15.

n = 3, R = *cis*-PhCOCH=C(Me)-:

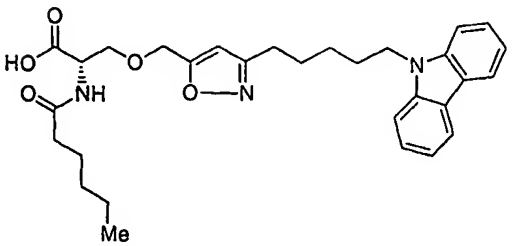


Yield, 21%; $[\alpha]_D$ +42.5 (c 0.15, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.09 (d, 2H, J = 7.8 Hz), 7.81-7.76 (m, 2H), 7.49-7.17 (m, 9H), 6.18 (s, 1H), 5.68 (s, 1H), 4.63 (s, 2H), 4.30 (t, 2H, J = 7.2 Hz), 4.27 (m, 1H), 3.95 (dd, 1H, J = 9.3, 3.3 Hz), 3.87 (dd, 1H, J = 9.3, 6.6 Hz), 2.55 (t, 2H, J = 7.5 Hz), 2.09 (s, 3H), 1.90-1.79 (m, 2H), 1.67-1.56 (m, 2H), 1.42-1.31 (m, 2H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 175.10, 169.79, 166.42, 164.72, 141.11, 140.91, 131.29, 128.82, 127.40, 126.23, 123.47, 120.75, 119.37, 103.35, 73.76, 64.69, 59.42, 43.19, 29.13, 28.47, 27.30, 26.25, 19.80.

n = 3, R = $CH_3CH_2CH_2CH_2CH_2CO$-:

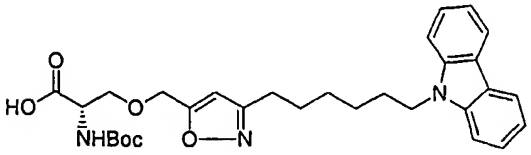


Yield, 87%; $[\alpha]_D$ +27.4 (c 1.35, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.07 (d, 2H, J = 7.8 Hz), 7.48-7.38 (m, 4H), 7.26-7.16 (m, 2H), 6.08 (s, 1H), 4.55 (s, 2H), 4.48 (br s, 1H), 4.31 (t, 2H, J = 7.2 Hz), 3.91 (dd, 1H, J = 9.3, 3.9 Hz), 3.81 (dd, 1H, J = 9.3, 3.0 Hz), 2.57 (t, 2H, J = 7.5 Hz), 2.24 (t, 2H, J = 7.5 Hz), 1.95-1.84 (m, 2H), 1.74-1.55 (m, 4H), 1.48-1.20 (m, 6H), 0.92-0.84 (m, 3H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 174.82, 169.55, 164.42, 140.97, 126.14, 123.35, 120.67, 119.26, 109.22, 103.41, 72.04, 64.31, 54.96, 43.11, 36.83, 31.88, 29.07, 28.41, 27.21, 26.18, 25.92, 22.86, 14.10.

n = 4, R = Boc-:

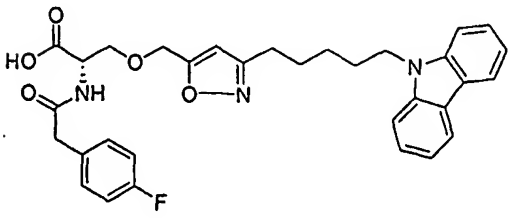


Yield, 83%; $[\alpha]_D$ +39 (c 0.54, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.08 (d, 2H, J = 7.8 Hz), 7.49-7.40 (m, 4H), 7.24-7.17 (m, 2H), 6.16 (s, 1H), 4.59 (s, 2H), 4.34 (t, 2H, J = 7.2 Hz), 4.23 (br s, 1H), 3.95-3.75 (m, 2H), 2.58 (t, 2H, J = 7.5 Hz), 1.95-1.80 (m, 2H), 1.70-1.55 (m, 2H), 1.50-1.30 (m, 13H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 174.89, 169.67, 164.66, 156.78, 141.02, 126.11, 123.34, 120.66, 119.22, 109.24, 103.32, 80.06, 72.33, 64.44, 55.80, 43.29, 29.41, 29.36, 28.55, 28.50, 27.40, 26.23.

n = 3, R = 4-F-PhCH_2CO-:

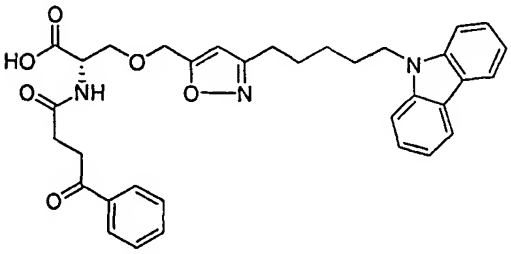


Yield, 63%; $[\alpha]_D$ +16.5 (c 1.15, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.10-8.04 (m, 2H), 7.48-7.40 (m, 4H), 7.32-7.16 (m, 4H), 7.03-6.92 (m, 2H), 6.02 (s, 1H), 4.51 (s, 2H), 4.44 (br s, 1H), 4.33 (t, 2H, J = 7.2 Hz), 3.90 (dd, 1H, J = 9.6, 4.5 Hz), 3.80 (dd, 1H, J = 9.6, 3.3 Hz), 3.58 and 3.53 (AB quart, 2H, J = 15.0 Hz), 2.57 (t, 2H, J = 7.5 Hz), 1.97-1.86 (m, 2H), 1.71-1.60 (m, 2H), 1.48-1.37 (m, 2H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 174.91, 172.24, 169.59, 164.45, 164.18 and 160.94, 141.00, 131.72 and 131.68, 131.44 and 131.34, 126.15, 123.37, 120.68, 119.27, 115.92 and 115.64, 109.24, 103.37, 71.96, 64.27, 55.37, 43.15, 42.71, 29.08, 28.43, 27.23, 26.21.

n = 3, R = $PhCOCH_2CH_2CO$-:

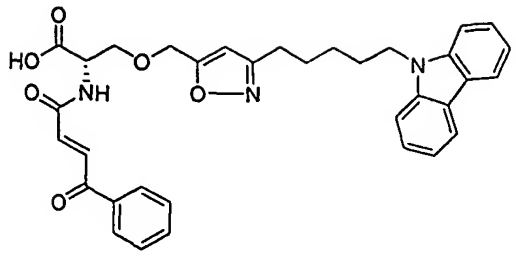


Yield, 72%; $[\alpha]_D$ +35.8 (c 1.3, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.10-7.91 (m, 4H), 7.56-7.37 (m, 7H), 7.24-7.15 (m, 2H), 6.12 (s, 1H), 4.58 (s, 2H), 4.48 (br s, 1H), 4.30 (t, 2H, J = 6.9 Hz), 3.97-3.80 (m, 2H), 3.40-3.24 (m, 2H), 2.68 (t, 2H, J = 6.9 Hz), 2.55 (t, 2H, J = 7.5 Hz), 1.93-1.82 (m, 2H), 1.70-1.58 (m, 2H), 1.45-1.34 (m, 2H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 200.29, 175.14, 173.42, 169.64, 164.49, 140.99, 137.11, 133.86, 129.12, 128.53, 126.15, 123.35, 120.68, 119.27, 109.24, 103.44, 72.09, 64.39, 55.28, 43.13, 34.43, 30.41, 29.08, 28.42, 27.23, 26.20.

n = 3, R = *trans*-$PhCOCH_2$=CH_2CO-:

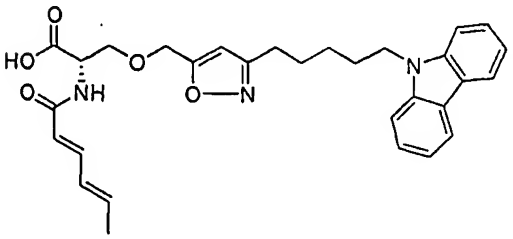


Yield, 59%; $[\alpha]_D$ +21.3 (c 0.63, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.10-7.95 (m, 4H), 7.89 (d, 1H, *J* = 15.3 Hz), 7.64-7.39 (m, 7H), 7.27-7.17 (m, 2H), 7.12 (d, 1H, *J* = 15.3 Hz), 6.13 (s, 1H), 4.59 (s, 3H), 4.33 (t, 2H, *J* = 6.9 Hz), 4.03-3.86 (m, 2H), 2.57 (t, 2H, *J* = 7.5 Hz), 1.95-1.84 (m, 2H), 1.71-1.60 (m, 2H), 1.48-1.36 (m, 2H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 191.20, 174.56, 169.69, 164.46, 140.97, 137.42, 136.48, 134.36, 133.40, 126.13, 123.33, 120.66, 119.25, 109.22, 103.38, 72.04, 64.35, 55.80, 43.15, 29.06, 28.39, 27.22, 26.20.

n = 3, R = *trans,trans*-MeCH=CHCH=CHCO-:

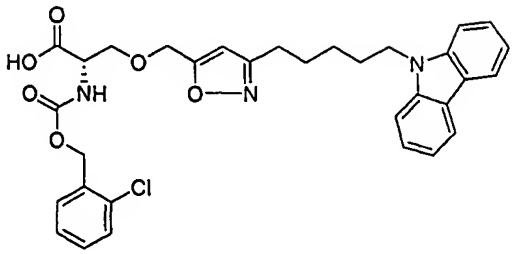


Yield, 41%; $[\alpha]_D$ +56 (c 0.34, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.09 (d, 2H, *J* = 7.8 Hz), 7.50-7.40 (m, 4H), 7.25-7.18 (m, 2H), 7.12 (dd, 1H, *J* = 15.3, 10.5 Hz), 6.22-5.99 (m, 3H), 5.92 (d, 1H, *J* = 15.3 Hz), 4.57 (s, 2H), 4.54 (br s, 1H), 4.35 (t, 2H, *J* = 7.2 Hz), 3.97 (dd, 1H, *J* = 9.6, 3.9 Hz), 3.85 (dd, 1H, *J* = 9.3, 2.7 Hz), 2.58 (t, 2H, *J* = 7.5 Hz), 1.98-1.85 (m, 2H), 1.79 (d, 3H, *J* = 6.0 Hz), 1.73-1.61 (m, 2H), 1.48-1.37 (m, 2H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 169.73, 167.58, 164.46, 162.45, 141.79, 140.99, 138.34, 130.42, 126.15, 123.35, 122.11, 120.68, 119.27, 109.23, 103.34, 72.18, 64.38, 55.31, 43.17, 29.08, 28.39, 27.21, 26.18, 18.60.

n =3, R = *o*-Cl-PhCH$_2$OCO-:

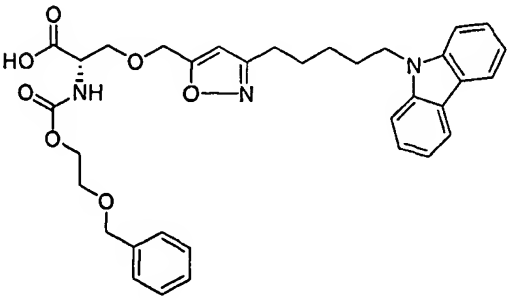


Yield, 73%; $[\alpha]_D$ +15.7 (c 1.8, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.07 (d, 2H, J = 7.8 Hz), 7.47-7.16 (m, 10H), 6.07 (s, 1H), 5.23 and 5.17 (AB quart, 2H, J = 12.6 Hz), 4.56 (s, 2H), 4.34-4.26 (m, 3H), 3.97-3.75 (m, 2H), 2.55 (t, 2H, J = 7.5 Hz), 1.94-1.83 (m, 2H), 1.68-1.57 (m, 2H), 1.45-1.34 (m, 2H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 174.69, 169.51, 164.44, 156.97, 140.95, 134.77, 133.44, 129.78, 129.72, 129.66, 127.42, 126.13, 123.32, 120.66, 119.25, 109.21, 103.38, 72.10, 64.36, 64.32, 56.34, 43.11, 29.05, 28.37, 27.19, 26.15.

n =3, R = PhCH$_2$OCH$_2$CH$_2$OCO-:



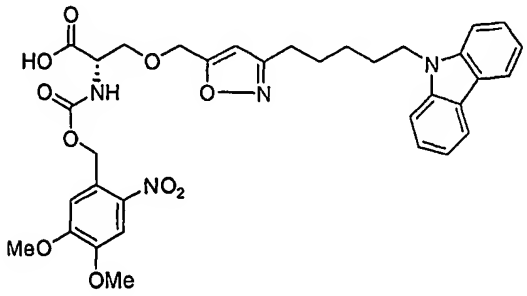
Yield, 69%; $[\alpha]_D$ +15.2 (c 1.6, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.08 (d, 1H, J = 7.8 Hz), 7.48-7.17 (m, 11H), 6.07 (s, 1H), 4.55 (s, 2H), 4.51 (s, 2H), 4.33-4.15 (m, 5H), 3.95-3.78 (m, 2H), 3.65 (t, 2H, J = 4.8 Hz), 2.55 (t, 2H, J = 7.5 Hz), 1.94-1.83 (m, 2H), 1.69-1.58 (m, 2H), 1.45-1.34 (m, 2H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 174.87, 169.54, 164.45, 157.26, 140.96, 138.31, 128.88,

128.27, 126.14, 123.33, 120.67, 119.26, 109.23, 103.38, 73.62, 72.15, 68.86, 64.58, 64.38, 56.30, 43.11, 29.06, 28.39, 27.18, 26.15.

n = 3, R = 2-NO_2-4,5-di-MeO-$PhCH_2OCO$-:

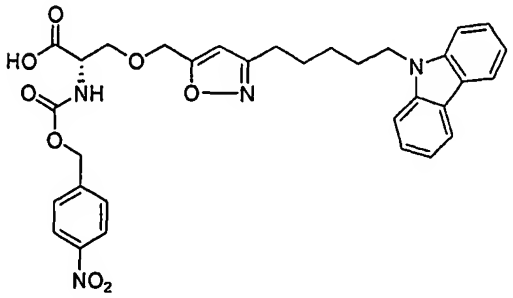


Yield, 63%; $[\alpha]_D$ +9.6 (c 1.2, MeOH-CH_2Cl_2 1:1).

^1H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.07 (d, 2H, J = 7.8 Hz), 7.68 (s, 1H), 7.48-7.38 (m, 4H), 7.23-7.16 (m, 2H), 7.14 (s, 1H), 6.09 (s, 1H), 5.49 (s, 2H), 4.58 (s, 2H), 4.37-4.27 (m, 3H), 3.97-3.85 (m, 8H), 2.57 (t, 2H, J = 7.5 Hz), 1.95-1.85 (m, 2H), 1.71-1.60 (m, 2H), 1.47-1.36 (m, 2H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 174.76, 169.51, 164.46, 156.77, 154.53, 148.47, 140.94, 139.73, 129.39, 126.13, 123.31, 120.64, 119.24, 110.08, 109.21, 108.53, 103.46, 72.15, 64.29, 64.01, 56.79, 56.56 (2 C), 43.11, 29.04, 28.38, 27.20, 26.16.

n = 3, R = *p*-NO_2-$PhCH_2OCO$-:



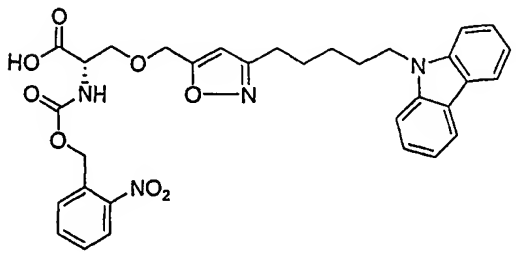
Yield, 57%; $[\alpha]_D$ +9.5 (c 1.0, MeOH-CH_2Cl_2 1:1).

^1H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.17 (d, 2H, J = 8.7 Hz), 8.08 (d, 2H, J = 7.8 Hz), 7.54-

7.38 (m, 6H), 7.23-7.16 (m, 2H), 6.09 (s, 1H), 5.19 (s, 2H), 4.57 (s, 2H), 4.33 (t, 2H, J = 6.9 Hz), 4.29 (br s, 1H), 3.95-3.75 (m, 2H), 2.57 (t, 2H, J = 7.5 Hz), 1.96-1.85 (m, 2H), 1.72-1.60 (m, 2H), 1.47-1.36 (m, 2H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 174.74, 169.54, 164.44, 156.77, 147.99, 145.06, 140.95, 128.35, 126.13, 124.07, 123.33, 120.66, 119.25, 109.22, 103.42, 72.17, 65.55, 64.33, 56.53, 43.12, 29.06, 28.39, 27.18, 26.17.

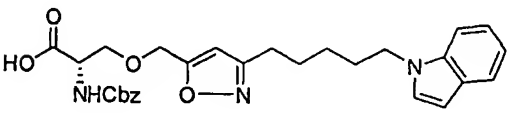
n = 3, R = *o*-NO_2-$PhCH_2OCO$-:



Yield, 68%; $[\alpha]_D$ +5.5 (c 0.55, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.11-8.03 (m, 3H), 7.72-7.62 (m, 2H), 7.49-7.40 (m, 5H), 7.24-7.17 (m, 2H), 6.11 (s, 1H), 5.51 (s, 2H), 4.59 (s, 2H), 4.34 (t, 2H, J = 6.9 Hz), 4.31 (br s, 1H), 3.95-3.83 (m, 2H), 2.59 (t, 2H, J = 7.5 Hz), 1.97-1.86 (m, 2H), 1.73-1.61 (m, 2H), 1.48-1.37 (m, 2H).

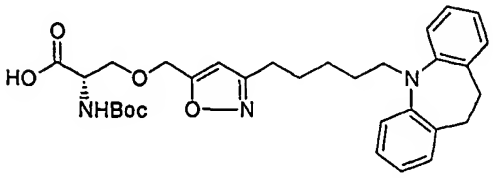
^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 174.28, 169.49, 164.44, 156.66, 140.94, 134.50, 133.83, 128.94, 126.11, 125.31, 123.30, 120.64, 119.22, 109.19, 103.42, 71.92, 64.36, 63.76, 56.18, 43.13, 29.04, 28.38, 27.18, 26.16.



Yield, 93%; $[\alpha]_D$ +14.8 (c 2.2, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 7.58 (d, 1H, J = 8.1 Hz), 7.38-7.22 (m, 6H), 7.16 (t, 1H, J = 7.2 Hz), 7.10 (d, 1H, J = 3.0 Hz), 7.05 (t, 1H, J = 7.5 Hz), 6.44 (d, 1H, J = 3.0 Hz), 6.07 (s, 1H), 5.09 (s, 2H), 4.55 (s, 2H), 4.37 (m, 1H), 4.11 (t, 2H, J = 7.2 Hz), 3.95-3.75 (m, 2H), 2.57 (t, 2H, J = 7.5 Hz), 1.90-1.79 (m, 2H), 1.69-1.57 (m, 2H), 1.38-1.27 (m, 2H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 176.26, 169.27, 164.54, 156.80, 148.88, 134.69, 130.20, 126.76, 122.82, 120.38, 103.37, 80.16, 72.11, 64.32, 55.84, 50.75, 32.64, 28.54, 28.33, 27.94, 27.08, 26.23.

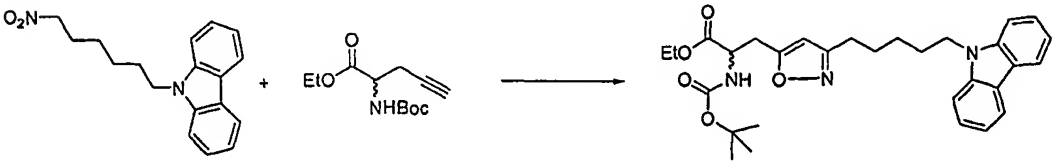


Yield, 89%; $[\alpha]_D$ +26.5 (c 1.7, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 7.15-7.04 (m, 6H), 6.93-6.87 (m, 2H), 6.12 (s, 1H), 4.57 (s, 2H), 4.19 (br s, 1H), 3.91 (dd, 1H, J = 9.3, 3.9 Hz), 3.79 (dd, 1H, J = 9.3, 3.0 Hz), 3.73 (t, 2H, J = 6.9 Hz), 3.14 (s, 4H), 2.58 (t, 2H, J = 7.5 Hz), 1.65-1.55 (m, 4H), 1.50-1.32 (m, 11H).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 176.26, 169.27, 164.54, 156.80, 148.88, 134.69, 130.20, 126.76, 122.82, 120.38, 103.37, 80.16, 72.11, 64.32, 55.84, 50.75, 32.64, 28.54, 28.33, 27.94, 27.08, 26.23.

Example 16



The nitro compound (455 mg, 1.54 mmol), the alkyne (370 mg, 1.54 mmol), and phenyl isocyanate (340 μL, 3.2 mmol) were dissolved in toluene (25 mL). Triethylamine (50 μL) was added and the reaction mixture was refluxed at 120 °C for 48 h under N_2. After cooled to room temperature, the reaction was quenched with 20 drops of water, and the mixture was stirred for an additional 3 h. The solid was removed by filtration, and the filtrate was concentrated. The residue was purified by chromatography with hexane-EtOAc (5:1) to give the isoxazole (600 mg, 75%) as syrup.

^{1}H NMR ($CDCl_3$) δ 8.09 (d, 2H, J = 7.8 Hz), 7.49-7.36 (m, 4H), 7.25-7.19 (m, 2H), 5.80 (s, 1H), 5.22 (d, 1H, J = 7.8 Hz), 4.62-4.55 (m, 1H), 4.28 (t, 2H, J = 7.2 Hz), 4.19 (qd, 2H, J =

7.2, 2.4 Hz), 3.30-3.14 (m, 2H), 2.55 (t, 2H, J = 7.5 Hz), 1.94-1.83 (m, 2H), 1.70-1.58 (m, 2H), 1.47-1.36 (m, 11H), 1.24 (t, 3H, J = 7.2 Hz).

^{13}C NMR ($CDCl_3$) δ 170.62, 163.59, 155.00, 140.25, 125.54, 122.71, 120.27, 118.70, 108.52, 102.41, 80.16, 61.83, 51.98, 42.72, 29.67, 28.51, 28.18, 27.82, 26.73, 25.76, 14.01.

Example 17

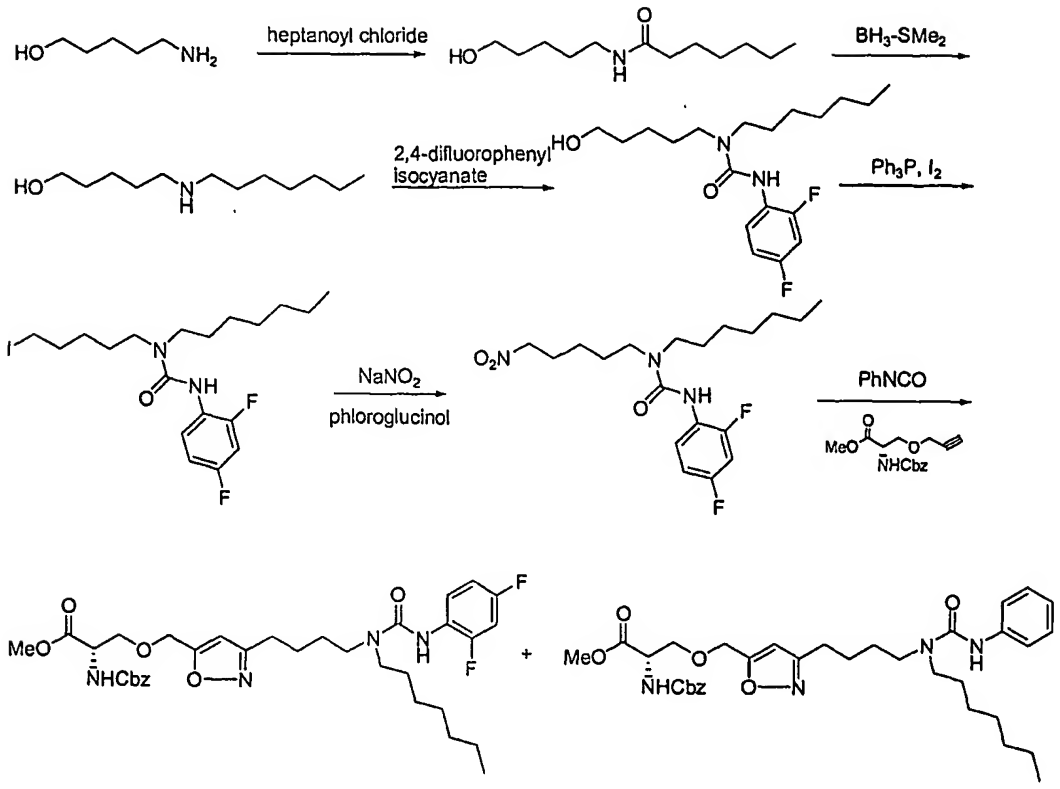
To a stirred solution of ethyl ester (55 mg, 0.1 mmol) in THF (2 mL) and water (2 mL) at 0 °C was added slowly a 2 N aqueous LiOH solution (0.2 mL, 0.4 mmol). The reaction mixture was minored by TLC. After completion the reaction mixture was neutralized with 0.5 N $NaHSO_4$ to pH 4, and diluted with EtOAc (100 mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography to give the acid, 52 mg (95%).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.08 (d, 2H, J = 7.8 Hz), 7.49-7.39 (m, 4H), 7.24-7.17 (m, 2H), 5.96 (s, 1H), 4.35 (m, 1H), 4.33 (t, 2H, J = 7.2 Hz), 3.36-3.08 (m, 2H), 2.55 (t, 2H, J = 7.5 Hz), 1.95-1.84 (m, 2H), 1.71-1.60 (m, 2H), 1.48-1.36 (m, 11H).

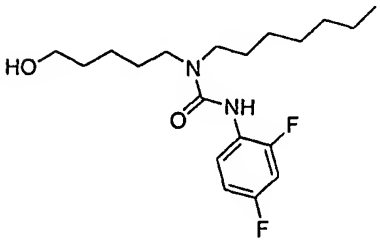
^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 175.70, 170.66, 164.46, 156.55, 140.95, 126.12, 123.33, 120.66, 119.24, 109.20, 102.70, 80.02, 54.09, 43.14, 30.53, 29.08, 28.52, 28.43, 27.25, 26.26.

Example 18

Overall Reaction Sequence



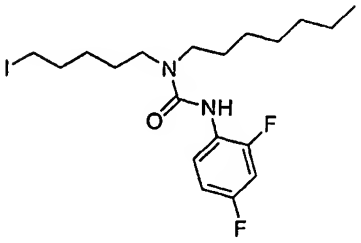
Preparation of



To a stirred solution of 5-amino-1-pentanol (3 g, 30 mmol) in chloroform (100 mL) and Et_3N (4.2 mL) at 0 °C was added slowly heptanoyl chloride (4.6 mL, 30 mmol). The reaction mixture was slowly warmed to room temperature and stirred overnight, then washed with brine. The organic phase was dried (Na_2SO_4), and concentrated. The residue

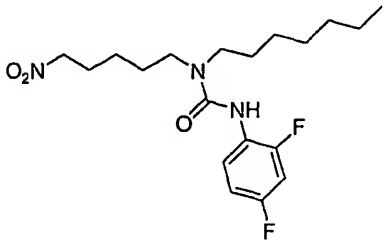
was purified by chromatography with EtOAc-MeOH (1:0 to 10:1) to give the amide (5.5 g, 85%). ^{1}H NMR ($CDCl_3$) δ 5.73 (br s, 1H), 3.65 and 3.61 (AB, 2H, J = 6.3 Hz), 3.27 and 3.22 (AB, 2H, J = 6.9 Hz), 2.16 (s, 1H), 2.14 (t, 2H, J = 7.5 Hz), 1.65-1.22 (m, 14H), 0.87 (t, 3H, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 173.32, 62.42, 39.24, 36.83, 32.12, 31.49, 29.35, 28.93, 25.74, 22.98, 22.46, 13.99.

To a stirred solution of the above amide (1g, 4.7 mmol) anhydrous THF (50 mL) at –30 °C was added 5 mL (50 mmol) of 10 M BH_3·SMe_2 complex. The reaction mixture was stirred at room temperature for 48 h, then quenched by adding 15 mL of MeOH. The mixture was stirred at room temperature for 1 h, then refluxed for 2 h. After cooled, the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (40 mL) and 2,4-difluorophenyl isocynate (590 μL, 5 mmol) was added. The reaction mixture was stirred at room temperature for 24 h, and then diluted with CH_2Cl_2 (50 mL). The mixture was washed with 1 N HCl, brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography with hexane-EtOAc (3:1 to 2:1) to give the urea (1.2 g, 72%). ^{1}H NMR ($CDCl_3$) δ 8.04-7.95 (m, 1H), 6.87-6.77 (m, 2H), 6.46 (d, 1H, J = 3.0 Hz), 3.62 (t, 2H, J = 6.3 Hz), 3.30 (t, 2H, J = 7.5 Hz), 3.26 (t, 2H, J = 7.5 Hz), 2.13 (s, 1H), 1.70-1.55 (6 H), 1.47-1.22 (m, 10H), 0.89 (t, 3H, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 157.44 (dd, J = 244, 12 Hz), 154.37, 152.34 (dd, J = 244, 12 Hz), 123.78 (dd, J = 10, 4 Hz), 122.64 (dd, J = 9, 3 Hz), 110.84 (dd, J = 21, 4 Hz), 103.02 (dd, J = 26, 24 Hz), 62.40, 47.85, 47.57, 32.16, 31.74, 29.04, 28.60, 28.20, 26.97, 23.17, 22.57, 14.08.

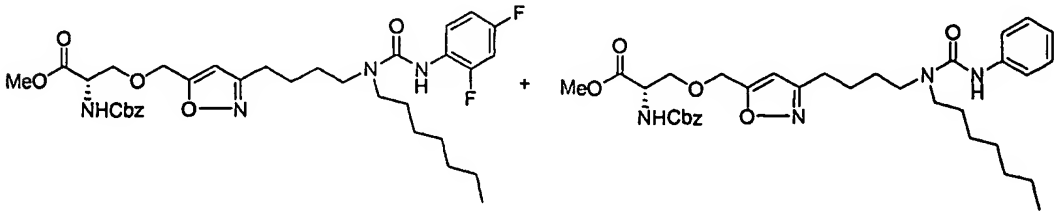


To a stirred solution of PPh_3 (780 mg, 3.0 mmol) in anhydrous CH_2Cl_2 (20 mL) was added I_2 (755 mg, 3.0 mmol) under N_2 at room temperature. After stirred at rt for 15 min, imidazole (240 mg, 3.5 mmol) was added in one portion, followed by addition of the above alcohol (500 mg, 1.35 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at rt for 4 h, then washed with 5% sodium thiosulfate, brine, dried (Na_2SO_4), and concentrated. The residue

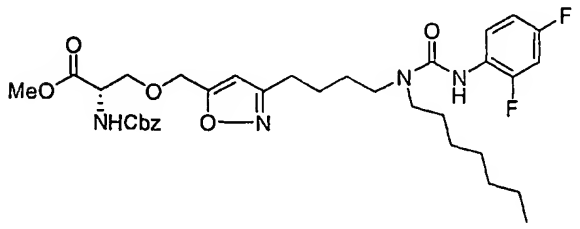
was purified by chromatography with hexane-EtOAc (10:1) to give the iodide (550 mg, 87%). ^{1}H NMR ($CDCl_3$) δ 8.10-8.01 (m, 1H), 6.89-6.79 (m, 2H), 6.41 (d, 1H, J = 3.0 Hz), 3.32 (t, 2H, J = 7.5 Hz), 3.28 (t, 2H, J = 7.8 Hz), 3.20 (t, 2H, J = 6.9 Hz), 1.94-1.80 (m, 2H), 1.71-1.58 (4 H), 1.52-1.22 (m, 10H), 0.89 (t, 3H, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 157.53 (dd, J = 244, 12 Hz), 154.35, 152.31 (dd, J = 244, 12 Hz), 123.94 (dd, J = 10, 4 Hz), 122.45 (dd, J = 9, 3 Hz), 110.99 (dd, J = 21, 4 Hz), 103.09 (dd, J = 26, 24 Hz), 47.97, 47.54, 33.00, 31.69, 28.99, 28.63, 27.79, 27.46, 26.93, 22.52, 14.02, 6.61.



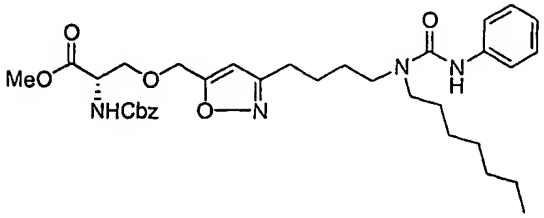
The above iodide (480 mg, 1.03 mmol) in DMSO (2 mL) was added to a mixture of $NaNO_2$ (175 mg, 2.54 mmol) and phloroglucinol (200 mg, 1.23 mmol) in DMSO (2 mL). The reaction mixture was stirred at room temperature for 48 h. After quenching of the reaction with ice-cold water (10 mL), the aqueous layer was extracted with EtOAc (15 mL × 3) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography with hexane-EtOAc (4:1) to give the desired product (150 mg, 38%). ^{1}H NMR ($CDCl_3$) δ 8.07-7.98 (m, 1H), 6.89-6.79 (m, 2H), 6.40 (d, 1H, J = 3.0 Hz), 4.40 (t, 2H, J = 6.9 Hz), 3.34 (t, 2H, J = 7.5 Hz), 3.26 (t, 2H, J = 7.8 Hz), 2.12-2.01 (m, 2H), 1.73-1.58 (4 H), 1.49-1.22 (m, 10H), 0.89 (t, 3H, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 157.49 (dd, J = 244, 12 Hz), 154.25, 152.27 (dd, J = 244, 12 Hz), 123.75 (dd, J = 10, 4 Hz), 122.50 (dd, J = 9, 3 Hz), 110.95 (dd, J = 21, 4 Hz), 103.08 (dd, J = 26, 24 Hz), 75.39, 48.04, 47.28, 31.75, 29.05, 28.71, 27.83, 27.09, 27.01, 23.71, 22.60, 14.11.



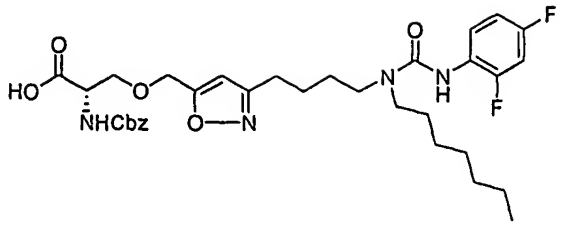
The above nitro compound (70 mg, 0.2 mmol), the alkyne (60 mg, 0.2 mmol), and phenyl isocyanate (50 μL) were dissolved in toluene (2 mL). Triethylamine (5 μL) was added and the reaction mixture was refluxed at 120 °C for 48 h under N_2. After cooled to room temperature, the reaction was quenched with 2 drops of water, and the mixture was stirred for an additional 2 h. The solid was removed by filtration, and the filtrate was concentrated. The residue was purified by chromatography with hexane-EtOAc (1:1) to give the isoxazoles (combined yield, 63%).



^{1}H NMR ($CDCl_3$) δ 8.06-7.97 (m, 1H), 7.32 (m, 5H), 6.88-6.79 (m, 2H), 6.43 (d, 1H, J = 3.3 Hz), 6.05 (s, 1H), 5.61 (d, 1H, J = 7.5 Hz), 5.12 (s, 2H), 4.60-4.49 (m, 3H), 3.96 (dd, 1H, J = 9.0, 3.0 Hz), 3.79 (dd, 1H, J = 9.0, 3.0 Hz), 3.75 (s, 3H), 3.34 (t, 2H, J = 6.9 Hz), 3.26 (t, 2H, J = 7.5 Hz), 2.70 (t, 2H, J = 6.9 Hz), 1.75-1.55 (m, 6H), 1.40-1.20 (m, 8H), 0.89 (t, 3H, J = 6.9 Hz).

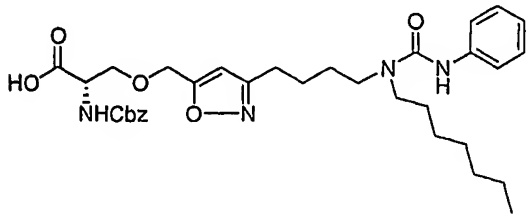


^{1}H NMR ($CDCl_3$) δ 7.46-7.23 (m, 9H), 7.04-6.97 (m, 1H), 6.49 (s, 1H), 6.05 (s, 1H), 5.62 (d, 1H, J = 8.1 Hz), 5.12 (s, 2H), 4.59-4.47 (m, 3H), 3.95 (dd, 1H, J = 9.3, 3.3 Hz), 3.76 (dd, 1H, J = 9.3, 3.3 Hz), 3.74 (s, 3H), 3.33 (t, 2H, J = 7.5 Hz), 3.25 (t, 2H, J = 7.8 Hz), 2.70 (t, 2H, J = 6.9 Hz), 1.80-1.50 (m, 6H), 1.40-1.20 (m, 8H), 0.88 (t, 3H, J = 6.9 Hz).



Yield, 73%.

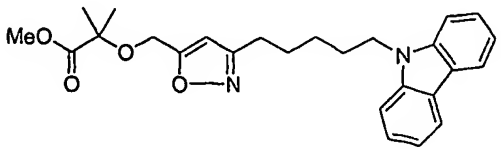
^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 7.59-7.50 (m, 1H), 7.40-7.25 (m, 5H), 6.93-6.81 (m, 2H), 6.23 (s, 1H), 5.10 (s, 2H), 4.60 (s, 2H), 4.32 (br s, 1H), 4.00-3.80 (m, 2H), 3.40-3.25 (m, 4H), 2.71 (t, 2H, J = 6.6 Hz), 1.75-1.55 (m, 6H), 1.40-1.20 (m, 8H), 0.90 (t, 3H, J = 6.3 Hz).



Yield, 87%; $[\alpha]_D$ +12.1 (c 1.65, MeOH-CH_2Cl_2 1:1).

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 7.39-7.23 (m, 9H), 7.05-6.98 (m, 1H), 6.24 (s, 1H), 5.10 (s, 2H), 4.59 (s, 2H), 4.34 (br s, 1H), 3.95-3.75 (m, 2H), 3.40-3.28 (m, 4H), 2.70 (t, 2H, J = 6.9 Hz), 1.75-1.50 (m, 6H), 1.40-1.20 (m, 8H), 0.89 (t, 3H, J = 6.9 Hz).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 174.16, 169.80, 164.51, 157.21, 140.05, 137.22, 129.09, 129.00, 128.58, 128.36, 123.68, 122.01, 103.56, 71.95, 67.29, 64.48, 55.98, 47.93, 47.25, 32.43, 29.77, 29.04, 28.23, 27.43, 26.03, 25.73, 23.15, 14.28.

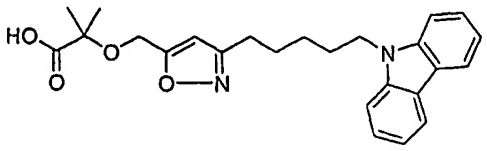


Yield, 92%; oil.

^{1}H NMR ($CDCl_3$) δ 8.09 (d, 2H, J = 7.8 Hz), 7.48-7.36 (m, 4H), 7.25-7.18 (m, 2H), 6.03 (s, 1H), 4.54 (s, 2H), 4.28 (t, 2H, J = 7.2H), 3.74 (s, 3H), 2.59 (t, 2H, J = 7.5 Hz), 1.94-1.83

(m, 2H), 1.72-1.61 (m, 2H), 1.49 (s, 6H), 1.48-1.38 (m, 2H).

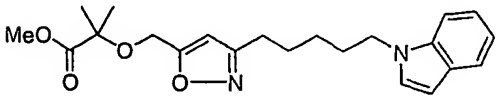
^{13}C NMR ($CDCl_3$) δ 174.41, 169.22, 163.51, 140.27, 125.55, 122.72, 120.27, 118.69, 108.54, 102.25, 78.36, 58.50, 52.23, 42.74, 28.55, 27.88, 26.74, 25.80, 24.60.



Yield, 95%;

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 8.06 (d, 2H, J = 7.8 Hz), 7.47-7.36 (m, 4H), 7.22-7.16 (m, 2H), 6.06 (s, 1H), 4.57 (s, 2H), 4.27 (t, 2H, J = 7.2H), 2.54 (t, 2H, J = 7.5 Hz), 1.91-1.80 (m, 2H), 1.67-1.56 (m, 2H), 1.49 (s, 6H), 1.43-1.32 (m, 2H).

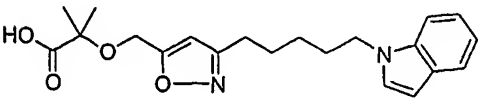
^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 177.49, 170.44, 164.41, 140.92, 126.11, 123.30, 120.65, 119.23, 109.19, 103.01, 79.13, 58.72, 43.09, 29.02, 28.38, 27.15, 26.14, 24.88.



Yield, 86%; oil.

^{1}H NMR ($CDCl_3$) δ 7.62 (dt, 1H, J = 7.8, 0.9 Hz), 7.35-7.06 (m, 4H), 6.48 (dd, 1H, J = 3.0, 0.9 Hz), 6.07 (s, 1H), 4.56 (s, 2H), 4.12 (t, 2H, J = 7.2H), 3.75 (s, 3H), 2.62 (t, 2H, J = 7.5 Hz), 1.92-1.81 (m, 2H), 1.73-1.62 (m, 2H), 1.50 (s, 6H), 1.44-1.33 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 174.46, 169.31, 163.55, 135.84, 128.52, 127.73, 121.31, 120.91, 119.16, 109.29, 102.26, 100.91.78.42, 58.56, 52.28, 46.17, 29.86, 27.76, 26.48, 25.85, 24.65.



Yield, 93%;

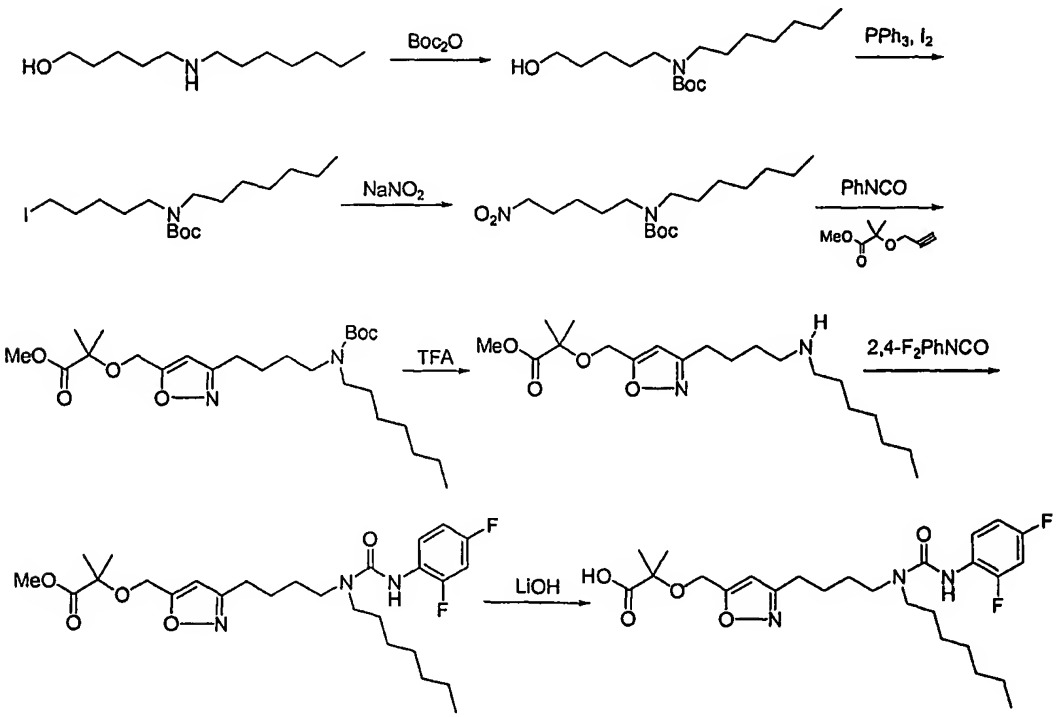
^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 7.58 (d, 1H, J = 8.1 Hz), 7.34 (d, 1H, J = 8.1 Hz), 7.20-7.02 (m, 3H), 6.45 (d, 1H, J = 3.3 Hz), 6.13 (s, 1H), 4.59 (s, 2H), 4.12 (t, 2H, J = 7.2H),

2.60 (t, 2H, J = 7.5 Hz), 1.91-1.80 (m, 2H), 1.71-1.60 (m, 2H), 1.49 (s, 6H), 1.40-1.29 (m, 2H).

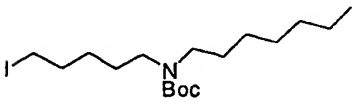
^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 177.75, 170.56, 164.43, 136.49, 129.17, 128.34, 121.72, 121.23, 119.53, 109.82, 102.98, 101.25, 79.25, 58.71, 46.47, 30.31, 28.20, 26.83, 26.15, 24.90.

Example 19

Overall Reaction Sequence



Physical Data for:

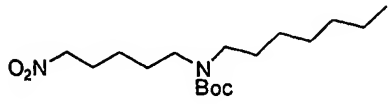


Yield, 86%.

^{1}H NMR ($CDCl_3$) δ 3.22-3.06 (m, 6H), 1.90-1.79 (m, 2H), 1.59-1.18 (m, 23H), 0.88 (t, 3H,

J = 6.9 Hz).

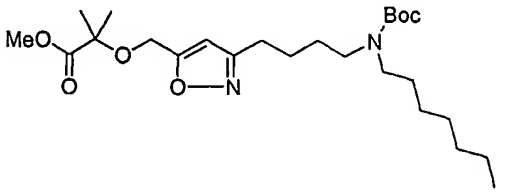
^{13}C NMR ($CDCl_3$) δ 155.55, 78.99, 47.08, 46.65, 33.11, 31.78, 29.03, 28.45, 27.75, 27.60 and 27.18, 26.80, 22.56, 14.05, 6.91.



Yield, 66%.

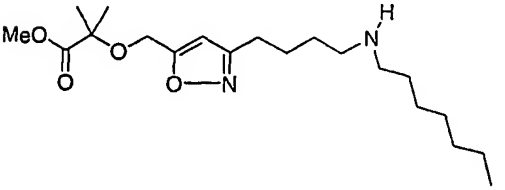
^{1}H NMR ($CDCl_3$) δ 4.39 (t, 3H, J = 7.2 Hz), 3.15 (m, 4H), 2.09-1.98 (m, 2H), 1.62-1.18 (m, 23H), 0.88 (t, 3H, J = 6.9 Hz).

^{13}C NMR ($CDCl_3$) δ 155.55, 79.14, 75.54, 47.11, 46.33, 31.79, 29.03, 28.43, 27.94 and 27.48, 27.07, 26.79, 23.52, 22.56.



Yield, 91%.

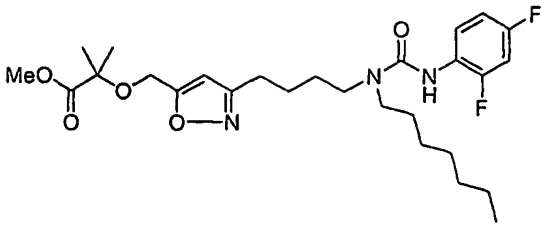
^{1}H NMR ($CDCl_3$) δ 6.14 (s, 1H), 4.58 (s, 2H), 3.76 (s, 3H), 3.18 (br s, 4H), 2.68 (t, 2H, J = 7.5 Hz), 1.75-1.20 (m, 29H), 0.89 (t, 3H, J = 6.9 Hz).



Yield, 98%;

^{1}H NMR ($CDCl_3$) δ 6.13 (s, 1H), 4.55 (s, 2H), 3.75 (s, 3H), 3.00-2.85 (m, 4H), 2.66 (t, 2H, J = 7.2 Hz), 1.85-1.60 (m, 6H), 1.49 (s, 6H), 1.40-1.15 (m, 8H), 0.86 (t, 3H, J = 6.9 Hz).

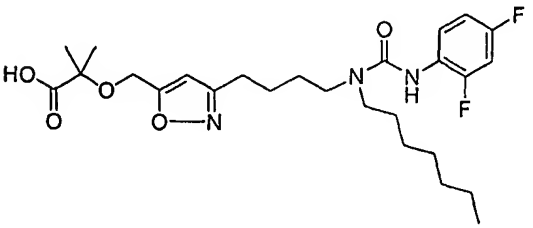
^{13}C NMR ($CDCl_3$) δ 174.46, 169.62, 162.82, 102.23, 78.40, 58.45, 52.25, 47.70, 47.12, 31.45, 28.61, 26.49, 25.87, 25.32, 25.23, 24.88, 24.59, 22.42, 13.93.



Yield, 84%;

^{1}H NMR ($CDCl_3$) δ 8.06-7.96 (m, 1H), 6.88-6.78 (m, 2H), 6.46 (d, 1H, J = 3.6 Hz), 6.14 (s, 1H), 4.57 (s, 2H), 3.75 (s, 3H), 3.34 (t, 2H, J = 7.2 Hz), 3.26 (t, 2H, J = 7.8 Hz), 2.71 (t, 2H, J = 7.2 Hz), 1.85-1.55 (m, 6H), 1.50 (s, 6H), 1.40-1.20 (m, 8H), 0.89 (t, 3H, J = 6.9 Hz).

^{13}C NMR ($CDCl_3$) δ 174.44, 169.48, 163.34, 157.66 (dd, J = 244, 12 Hz), 154.45, 152.55 (dd, J = 244, 12 Hz), 123.90 (dd, J = 10, 4 Hz), 122.80 (dd, J = 9, 3 Hz), 110.94 (dd, J = 21, 4 Hz), 103.12 (dd, J = 26, 24 Hz), 102.29, 78.40, 58.56, 52.27, 47.85, 47.16, 31.69, 28.98, 28.55, 27.78, 26.91, 25.60, 25.34, 24.62, 22.52, 14.01.



Yield, 95%.

^{1}H NMR (CD_3OD-$CDCl_3$ 1:1) δ 7.59-7.967.50 (m, 1H), 6.94-6.82 (m, 2H), 6.26 (s, 1H), 4.63 (s, 2H), 3.37 (t, 2H, J = 6.9 Hz), 3.31 (t, 2H, J = 7.8 Hz), 2.73 (t, 2H, J = 6.9 Hz), 1.80-1.56 (m, 6H), 1.50 (s, 6H), 1.42-1.22 (m, 8H), 0.90 (t, 3H, J = 6.9 Hz).

^{13}C NMR (CD_3OD-$CDCl_3$ 1:1) δ 177.58, 170.76, 164.31, 159.92 (dd, J = 245, 12 Hz), 156.71, 156.05 (dd, J = 245, 12 Hz), 127.15 (d, J = 8 Hz), 123.82, 111.21 (dd, J = 22, 4 Hz), 104.08 (t, J = 25 Hz), 103.04, 79.22, 58.79, 48.06, 47.39, 32.29, 29.61, 28.88, 28.11, 27.32, 26.00, 25.69, 24.90, 23.04, 14.23.

Example 20

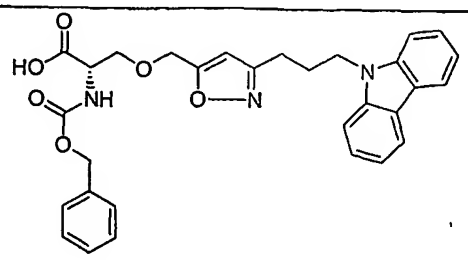
PPAR Isoform Screening

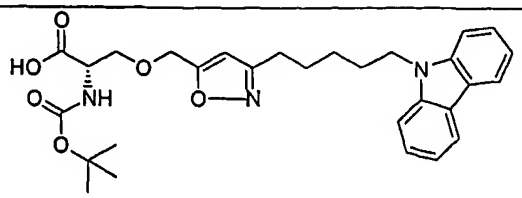
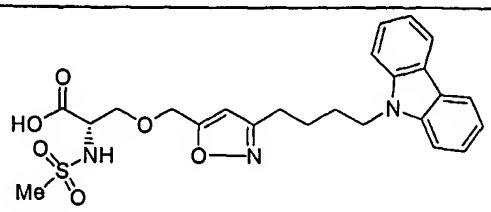
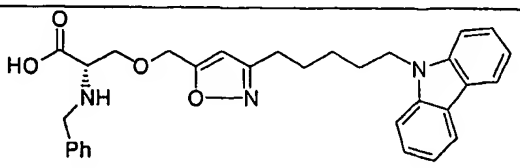
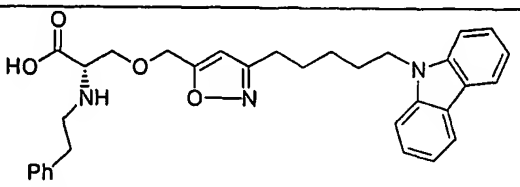
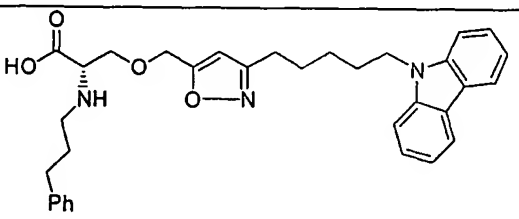
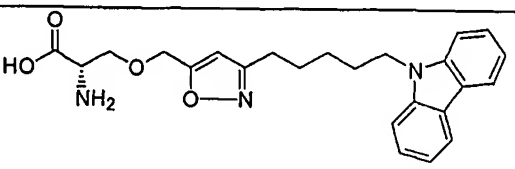
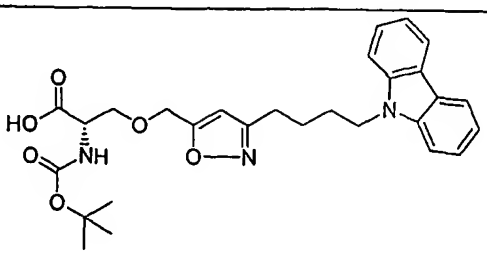
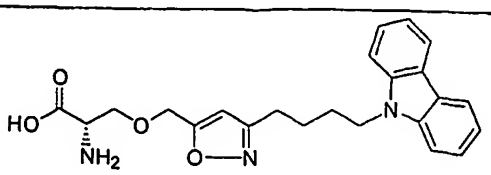
Chimeric GAL4-PPAR-dependent reporter gene assays were used to determine PPAR isoform selectivity of the tested ligands. The GAL4-PPAR plasmid is a fusion protein of amino acids 1-76 of the glucocorticoid receptor fused to amino acids 1-147 of the

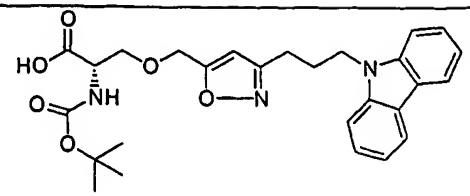
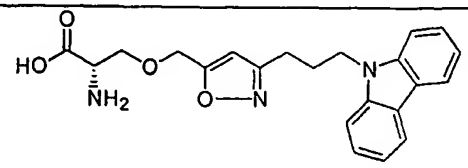
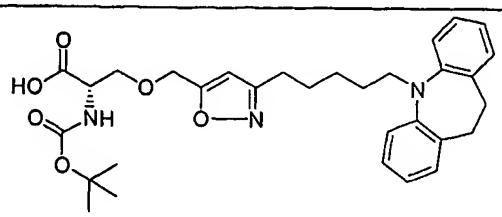
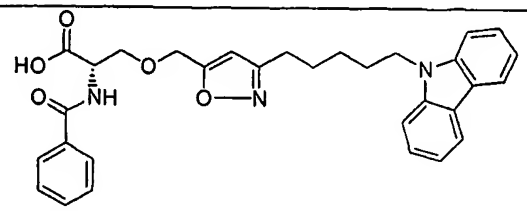
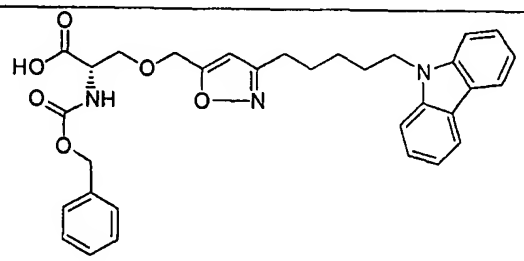
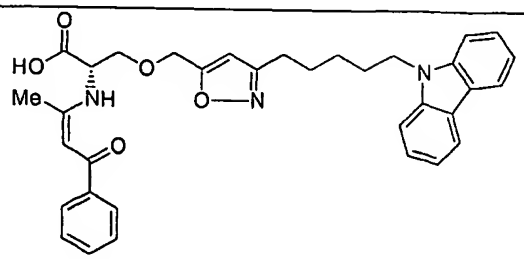
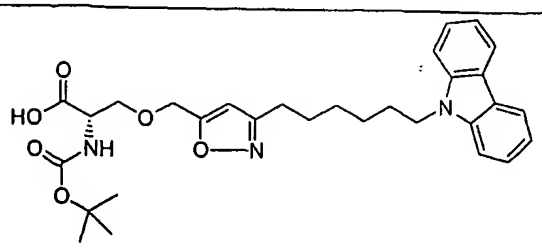
yeast transcription factor GAL4 DNA-binding domain, which is fused C-terminally to either amino acids 167-468, 138-440 and 174-475 of the murine PPARα, δ or γ ligand-binding domain. This assay measures PPAR-dependent transcriptional activation independently of endogenous PPAR activity.

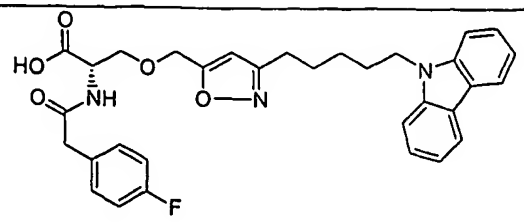
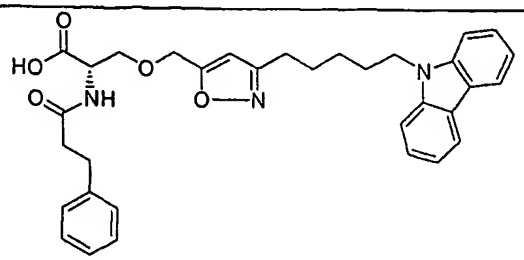
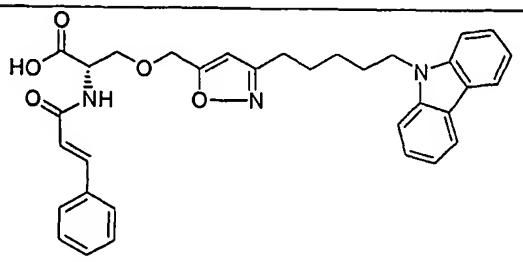
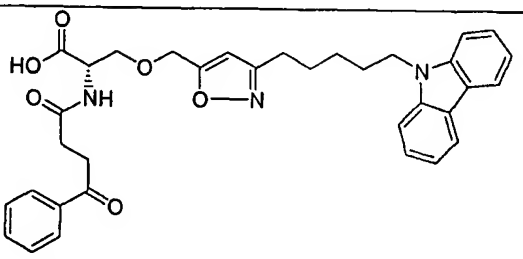
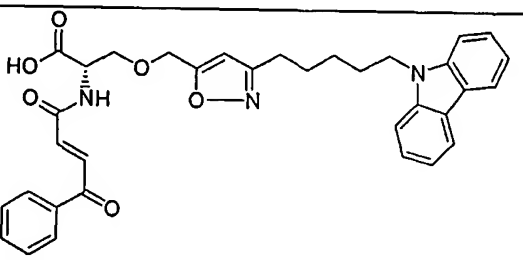
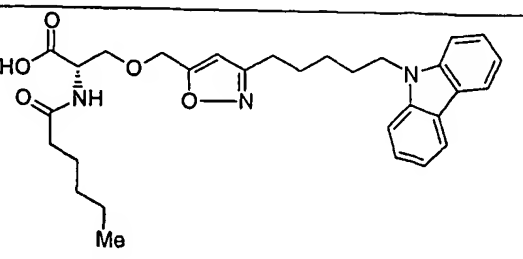
The chimeric receptor plasmid is cotransfected with a firefly luciferase reporter plasmid containing five copies of the GAL4 UAS response element upstream to the tk promoter. Upon binding of the PPAR ligand to the receptor, GAL4-PPAR binds to the UAS elements and activates transcription of the luciferase reporter gene. Luciferase activity is determined with the Dual Luciferase Assay (Promega) that measures the activity of firefly luciferase as well as *Renilla* luciferase, which is cotransfected with the PPAR receptor and firefly luciferase plasmids to correct for transfection efficiency. Human embryo fibroblast 293T cells are grown in 24-well plates in DMEM medium containing 10% delipidated fetal calf serum (Sigma-Aldrich Chemical Co.) and transfected using calcium phosphate (Profection, Promega) and 10 ng of PPAR receptor plasmid, 100 ng of firefly luciferase plasmid, and 10 ng of *Renilla* luciferase plasmid. The test ligand is added 24 hr after transfection at concentrations of 0.1-10.0 μM in DMSO so that the final concentration of DMSO is 0.1%, a concentration that is noncytotoxic. Luciferase activity is read 24 hr after drug addition. The PPAR agonist standards, WY14643 (Wyeth), L-165041 (Merck) and GW7845 (SmithKlineGlaxo) will be included at 5 μM as positive controls for PPARα, δ and γ, respectively. These constructs have been kindly provided by Dr. Steven Kliewer, SmithKlineGlaxo.

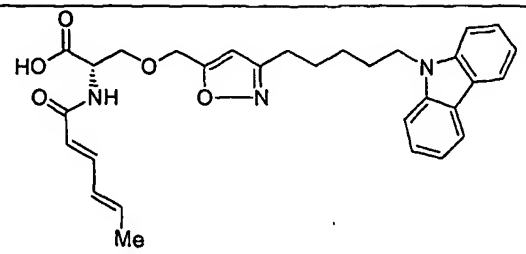
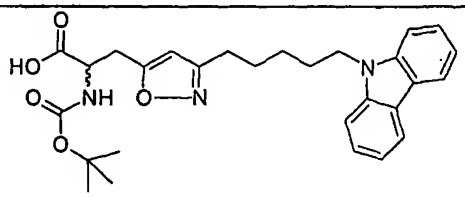
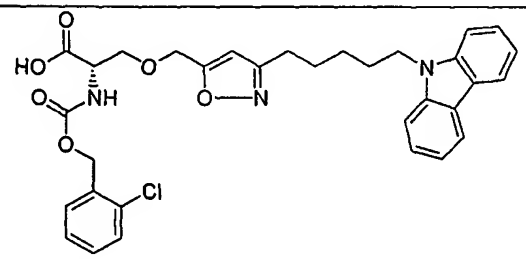
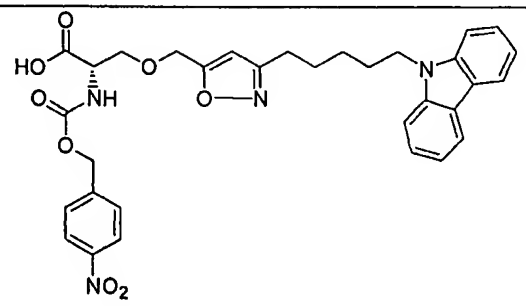
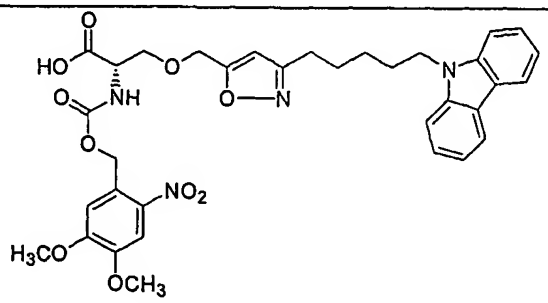
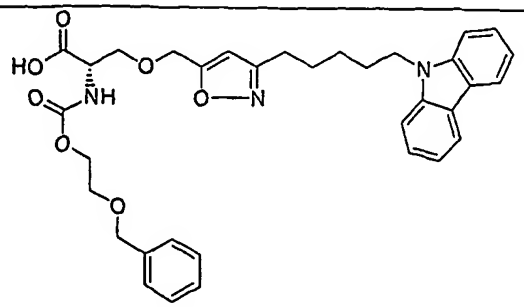
Example 21

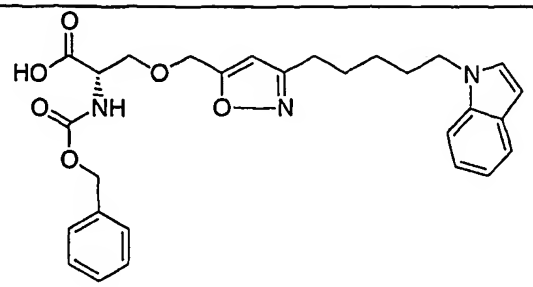
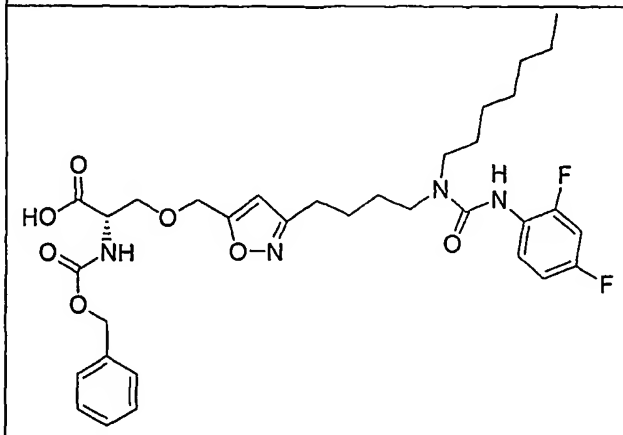
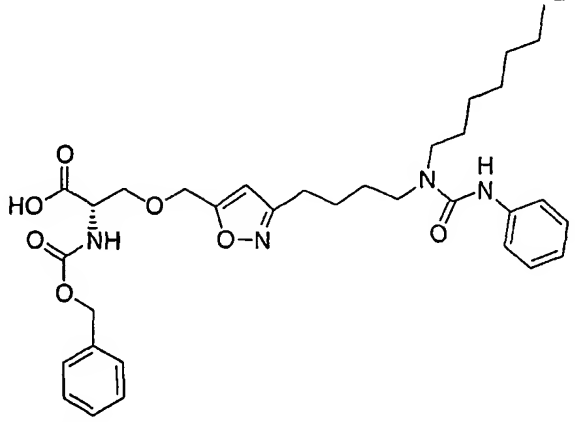
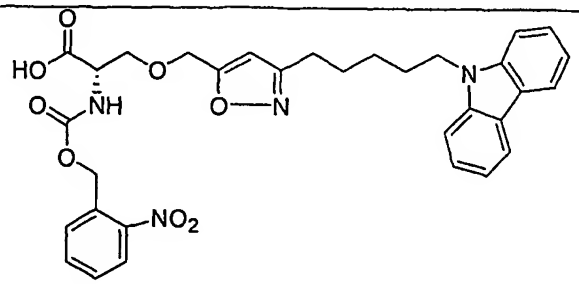
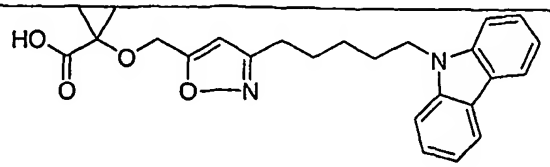
Compound	ID	PPARα	PPARγ	PPARδ
	ZW-40	+	0	0

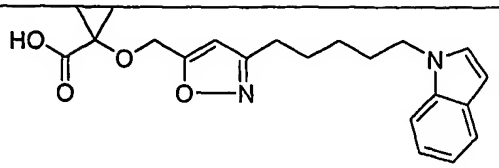
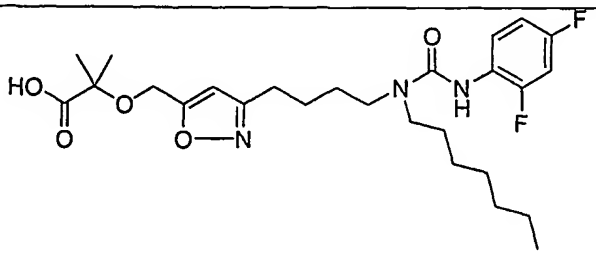
	ZW-41	(152%)	12%	0
	ZW-42	0	0	0
	ZW-43	0	0	0
	ZW-44	0	0	0
	ZW-45	0	0	0
	ZW-46	0	0	0
	ZW-47	+	0	0
	ZW-48	0	0	0

	ZW-49	0	0	0
	ZW-50	0	0	0
	ZW-51	0.4%	12%	0
	ZW-52	0	3%	0
	ZW-53	(175%)	2%	0
	ZW-54	0	18%	0
	ZW-55	118%	15%	0

	ZW-56	+	0	0
	ZW-57	0	0	0
	ZW-58	0	0	0
	ZW-59	0	0	0
	ZW-60	0	0	0
	ZW-61	0	0	0

	ZW-62	0	0	0
	ZW-63	0	0	0
	ZW-64	160%	0	0
	ZW-65	0	0	0
	ZW-66	0	0	0
	ZW-67	0	0	0

	ZW-68	0	0	55%
	ZW-69	39%	0	40%
	ZW-70	109%	0	0
	ZW-71			
	ZW-72			

	ZW-73			
	ZW-74			

Luciferase assay for drug screening on 293T cells after 24hrs transfection with PPARγ

	No ligands	Ligands		No ligands		Ligands	
Negative ctr	104314	94620		100214	108414	93688	95552
ZW-40		239484	1			278101	200867
ZW-41		712553	2			682335	742771
ZW-42		182549	3			169558	195540
GW7845		1586715				1674340	1499090

Luciferase assay for drug screening on 293T cells after 24hrs transfection with PPARδ

	No ligands	Ligands		No ligands		Ligands	
Negative ctr	74770.5	214143		77964	71577	226613	201673
ZW-40		165120.5	1			179030	151211
ZW-41		147332.5	2			142705	151960
ZW-42		165625.5	3			171204	160047
L16504-1		7749903				7474736	8025069

Luciferase assay for drug screening on 293T cells after 24hrs transfection with PPARα

	No ligands	Ligands		No ligands		Ligands	
Negative ctr	48722	1775420		48073	49371	1743158	1807682
ZW-40		3439495	1			3426729	3452261
ZW-41		16183511	2			16116701	16250321
ZW-42		1212357	3			1245684	1179030
WY14643		12970801				13036351	12905251

Incorporation By Reference

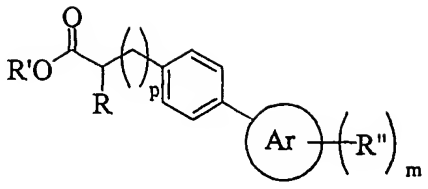
All of the patents and publications cited herein are hereby incorporated by reference.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

We claim:

1. A compound of formula **I**:



I

wherein

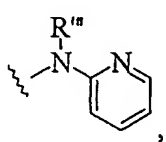
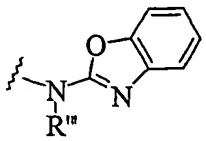
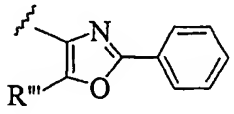
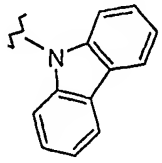
R' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, or an alkali metal cation;

R is H, C_1-C_6 alkyl, aryl, C_1-C_6 alkoxyl, C_4-C_{10} aryloxyl, -NHCO(C_1-C_6 alkyl), -NHCO(C_4-C_{10} aryl), -$NHSO_2$(C_1-C_6 alkyl), or -$NHSO_2$(C_4-C_{10} aryl);

Ar is a 5-10 membered aryl or heteroaryl ring, wherein the heteroaryl ring contains 1 to 3 heteroatoms selected from the group consisting of O, S, and N;

R" is -$(L)_nX$;

L, independently for each occurrence is -CH_2-, O, N, or S;

X is C_1-C_6 alkoxyl, C_4-C_{10} aryloxyl, -CO_2(C_1-C_6 alkyl), -CO_2(C_4-C_{10} aryl), -C(O)NH(C_1-C_6 alkyl), -C(O)NH(C_4-C_{10} aryl),  ,  ,  , or  ;

R''' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, -SO_2(C_1-C_6 alkyl), -SO_2(C_4-C_{10} aryl), -C(O)(C_1-C_6 alkyl), or -C(O)(C_4-C_{10} aryl);

m is an integer from 0 to 5 inclusive;

n is an integer from 0 to 6 inclusive; and

p is an integer from 0 to 6.

2. The compound of claim 1, wherein R' is H.

3. The compound of claim 1, wherein Ar is selected from the group consisting of phenyl, thiophenyl, and pyrrolyl.

4. The compound of claim 1, wherein p is 1.

5. The compound of claim 1, wherein m is 1.

6. The compound of claim 1, wherein L is $-CH_2-$ and n is 1, 2, 3, or 4.

7. The compound of claim 1, wherein X is $-OCH_3$ or $-CO_2CH_3$.

8. The compound of claim 1, wherein R is selected from the group consisting of $-OCH_2CH_3$, $-NHCOCH_3$, and $-NHSO_2CH_3$.

9. The compound of claim 1, wherein R' is H; p is 1; m is 1; Ar is phenyl; R is $-OCH_2CH_3$; L is $-CH_2-$; n is 4; and X is $-OCH_3$.

10. The compound of claim 1, wherein R' is H; p is 1; m is 1; Ar is phenyl; R is $-NHCOCH_3$; L is $-CH_2-$; n is 4; and X is $-OCH_3$.

11. The compound of claim 1, wherein R' is H; p is 1; m is 1; Ar is phenyl; R is $-OCH_2CH_3$; L is $-CH_2-$; n is 3; and X is $-OCH_3$.

12. The compound of claim 1, wherein R' is H; p is 1; m is 1; Ar is phenyl; R is $-OCH_2CH_3$; L is $-CH_2-$; n is 2; and X is $-CO_2CH_3$.

13. The compound of claim 1, wherein R' is H; p is 1; m is 1; Ar is phenyl; R is $-NHSO_2CH_3$; L is $-CH_2-$; n is 2; and X is $-CO_2CH_3$.

14. The compound of claim 1, wherein R' is H; p is 1; m is 1; Ar is thiophenyl; R is $-OCH_2CH_3$; L is $-CH_2-$; n is 4; and X is $-OCH_3$.

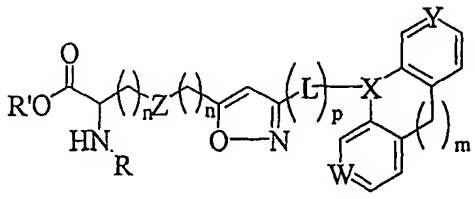
15. The compound of claim 1, wherein R' is H; p is 1; m is 1; Ar is pyrrolyl; R is $-OCH_2CH_3$; L is $-CH_2-$; n is 4; and X is $-OCH_3$.

16. The compound of claim 1, wherein R' is H; p is 1; m is 1; Ar is thiophenyl; R is OCH_2CH_3; L is $-CH_2-$; n is 2; and X is $-OCH_3$.

17. The compound of claim 1, wherein R' is H; p is 1; m is 1; Ar is pyrrolyl; R is $-OCH_2CH_3$; L is $-CH_2-$; n is 2; and X is $-OCH_3$.

18. The compound of claim 1, wherein R' is H; p is 1; m is 1; Ar is thiophenyl; R is $-OCH_2CH_3$; L is $-CH_2-$; n is 1; and X is $-OCH_3$.

19. A compound of formula **II**:



II

wherein

R' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, or an alkali metal cation;

R is H, C_1-C_6 alkyl, C_4-C_{10} aryl, $-CO(C_1$-C_6 alkyl), $-CO(C_4$-C_{10} aryl), -CO(aralkyl), $-CO(aryl(C_2$-C_6 alkenyl)), $-CO(C_1$-C_6 alkyl)C(O)aryl, $-CO(C_2$-C_6 alkenyl)C(O)aryl, $-CO(C_2$-C_6 alkenyl)alkyl, $-CO_2(C_1$-C_6 alkyl)Oaralkyl, $-SO_2(C_1$-C_6 alkyl), $-SO_2(C_4$-C_{10} aryl), $-CO_2$(aralkyl), $-CO_2C(C_1$-C_6 alkyl)$_3$, aralkyl, or $-C(C_1$-C_6 alkyl)=CHC(O)aryl;

W is CH or N;

X is CH or N;

Y is CH or N;

Z is a bond, O, S, or NR;

L, independently for each occurrence, is $-CH_2-$, O, N, or S;

n independently for each occurrence, is an integer from 1 to 6 inclusive;

m is an integer from 0 to 2 inclusive; and

p is an integer from 1 to 6 inclusive.

20. The compound of claim 19, wherein R' is H.

21. The compound of claim 19, wherein n is 1.

22. The compound of claim 19, wherein L is $-CH_2-$ and p is 3, 4, 5 or 6.

23. The compound of claim 19, wherein m is 0.

24. The compound of claim 19, wherein Z is O.

25. The compound of claim 19, wherein X is N.

26. The compound of claim 19, wherein Y is CH.

27. The compound of claim 19, wherein Y is N.

28. The compound of claim 19, wherein R is selected from the group consisting of H, CH_3, $-SO_2CH_3$, $-SO_2Ph$, $-COCH_3$, -COPh, $-CO_2CH_2Ph$, $-CO_2C(CH_3)_3$, $-CH_2Ph$, $-CH_2CH_2Ph$, $-CH_2CH_2CH_2Ph$, and -C(Me)=CHCOPh.

29. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, L is $-CH_2-$, p is 5, Y is CH, and R is $-CH_3$.

30. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, L is $-CH_2-$, p is 5, Y is CH, and R is $-SO_2CH_3$.

31. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, L is $-CH_2-$, p is 3, Y is N, and R is $-CH_3$.

32. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, L is $-CH_2-$, p is 3, Y is N, and R is $-SO_2CH_3$.

33. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, L is $-CH_2-$, p is 3, Y is N, and R is $-SO_2Ph$.

34. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, L is $-CH_2-$, p is 3, Y is N, and R is $-COCH_3$.

35. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is $-CH_2-$, p is 3, and R is $-CO_2CH_2Ph$.

36. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is $-CH_2-$, p is 3, and R is $-CO_2C(CH_3)_3$.

37. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is $-CH_2-$, p is 3, and R is H.

38. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is $-CH_2-$, p is 4, and R is $-SO_2CH_3$.

39. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is $-CH_2-$, p is 4, and R is $-CO_2C(CH_3)_3$.

40. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is $-CH_2-$, p is 4, and R is H.

41. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is $-CH_2-$, p is 5, and R is $-CO_2C(CH_3)_3$.

42. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is $-CH_2-$, p is 5, and R is $-CH_2Ph$.

43. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is $-CH_2-$, p is 5, and R is $-CH_2CH_2Ph$.

44. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is -

CH_2-, p is 5, and R is -$CH_2CH_2CH_2Ph$.

45. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is -CH_2-, p is 5, and R is H.

46. The compound of claim 19, wherein R' is H, m is 2, n is 1, X is N, Y is CH, L is -CH_2-, p is 5, and R is -$CO_2C(CH_3)_3$.

47. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is -CH_2-, p is 5, and R is -COPh.

48. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is -CH_2-, p is 5, and R is -CO_2CH_2Ph.

49. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is -CH_2-, p is 5, and R is -$C(CH_3)$=CHCOPh.

50. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, L is -CH_2-, p is 6, and R is -$CO_2C(CH_3)_3$.

51. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is -CH_2-, p is 5, and R is -CO(aralkyl).

52. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is -CH_2-, p is 5, and R is -$COCH_2$(4-fluorophenyl).

53. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is -CH_2-, p is 5, and R is -$COCH_2CH_2Ph$.

54. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is -CH_2-, p is 5, and R is -CO(aryl(C_2-C_6 alkenyl)).

55. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is -COCH=CHPh.

56. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-CO(C_1-C_6$ alkyl)C(O)aryl.

57. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-COCH_2CH_2C(O)$aryl.

58. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-COCH_2CH_2C(O)$Ph.

59. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-CO(C_2-C_6$ alkenyl)C(O)aryl.

60. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is -COCH=CHC(O)aryl.

61. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is -COCH=CHC(O)Ph.

62. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-CO(CH_2)_4CH_3$.

63. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-CO(C_2-C_6$ alkenyl)alkyl.

64. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-COCH=CHCH=CHCH_3$.

65. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is $-CH_2-$, p is 5, and R is $-CO_2C(CH_3)_3$.

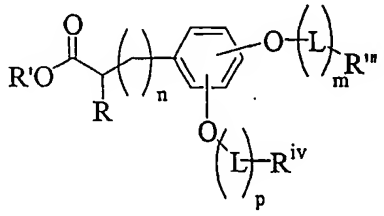
66. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is -CH_2-, p is 5, and R is -CO_2(aralkyl).

67. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is -CH_2-, p is 5, and R is -CO_2CH_2-(2-chorophenyl).

68. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is -CH_2-, p is 5, and R is -CO_2CH_2-(4-nitrophenyl) or -CO_2CH_2-(2-nitrophenyl).

69. The compound of claim 19, wherein R' is H, m is 0, n is 1, X is N, Y is CH, W is CH, L is -CH_2-, p is 5, and R is -CO_2CH_2-(2-nitro-4,5-dimethoxyphenyl).

70. A compound of formula **III**:



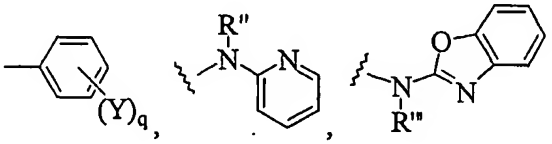
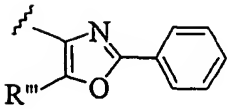
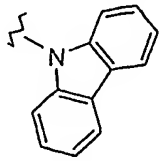
III

wherein

R' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, or an alkali metal cation;

R is H or NHR";

R" is H, C_1-C_6 alkyl, C_4-C_{10} aryl, -SO_2(C_1-C_6 alkyl), -SO_2(C_4-C_{10} aryl), -C(O)(C_1-C_6 alkyl), or -C(O)(C_4-C_{10} aryl);

R''' and R^{iv}, independently, are  ,  , or  ;

wherein,

Y is $-CF_3$ or $-(C_1-C_6$ alkyl)$-O-(C_1-C_6$ alkyl);

R''' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, $-SO_2(C_1-C_6$ alkyl), $-SO_2(C_4-C_{10}$ aryl), $-C(O)(C_1-C_6$ alkyl), or $-C(O)(C_4-C_{10}$ aryl); and

q is an integer from 0 to 5 inclusive;

L, independently for each occurrence, is $-CH_2-$, O, N, or S.

n is an integer from 0 to 5 inclusive;

m is, independently for each occurrence, an integer from 0 to 6 inclusive; and

p is an integer from 1 to 5 inclusive.

71. The compound of claim 70, wherein R' is H.

72. The compound of claim 70, wherein R is H.

73. The compound of claim 70, wherein R is NHR".

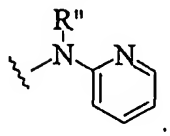
74. The compound of claim 70, wherein n is 1.

75. The compound of claim 70, wherein L is $-CH_2-$.

76. The compound of claim 70, wherein m is 0, 2, 3, or 4.

77. The compound of claim 70, wherein p is 2, 3, or 4.

78. The compound of claim 70, wherein R''' is Ph, *p*-$C_6H_4CF_3$, *p*-$C_6H_4CH_2CH_2OCH_3$,



or .

79. The compound of claim 70, wherein R^{iv} is -Ph, *p*-$C_6H_4CF_3$, or *p*-$C_6H_4CH_2CH_2OCH_3$.

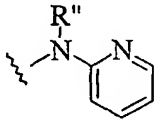
80. The compound of claim 70, wherein R' is H, R is H, n is 1, m is 0, L is $-CH_2-$, p is 2, R''' is Ph, and R^{iv} is Ph.

81. The compound of claim 70, wherein R' is H, R is H, n is 1, m is 0, L is -CH_2-, p is 2, R''' is *p*-$C_6H_4CF_3$, and R^{iv} is Ph.

82. The compound of claim 70, wherein R' is H, R is H, n is 1, m is 0, L is -CH_2-, p is 2, R''' is *p*-$C_6H_4CH_2CH_2OCH_3$, and R^{iv} is *p*-$C_6H_4CF_3$.

83. The compound of claim 70, wherein R' is H, R is H, n is 1, m is 0, L is -CH_2-, p is 2, R''' is *p*-$C_6H_4CH_2CH_2OCH_3$, and R^{iv} is *o*-$C_6H_4CF_3$.

84. The compound of claim 70, wherein R' is H, R is H, n is 1, m is 0, L is -CH_2-, p is 3, R''' is Ph, and R^{iv} is Ph.

85. The compound of claim 70, wherein R' is H, R is H, n is 1, m is 3, L is -CH_2-, p is 2, R''' is  , wherein R" is -CH_3, and R^{iv} is Ph.

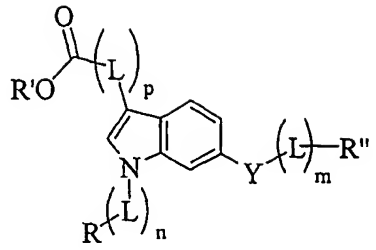
86. The compound of claim 70, wherein R' is H, R is NHR", wherein R" is -CH_3, n is 1, m is 4, L is -CH_2-, p is 4, R''' is *p*-$C_6H_4CF_3$, and R^{iv} is *p*-$C_6H_4CF_3$.

87. The compound of claim 70, wherein R' is H, R is NHR", wherein R" is -CH_3, n is 1, m is 3, L is -CH_2-, p is 3, R''' is *p*-$C_6H_4CF_3$, and R^{iv} is *p*-$C_6H_4CF_3$.

88. The compound of claim 70, wherein R' is H, R is NHR", wherein R" is -SO_2CH_3, n is 1, m is 3, L is -CH_2-, p is 3, R''' is *p*-$C_6H_4CF_3$, and R^{iv} is *p*-$C_6H_4CF_3$.

89. The compound of claim 70, wherein R' is H, R is NHR", wherein R" is -CH_3, n is 1, m is 2, L is -CH_2-, p is 2, R''' is *p*-$C_6H_4CF_3$, and R^{iv} is *p*-$C_6H_4CF_3$.

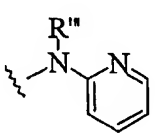
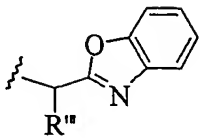
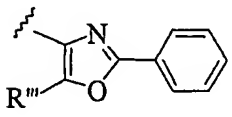
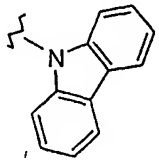
90. A compound of formula IV:



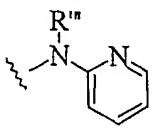
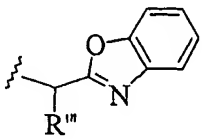
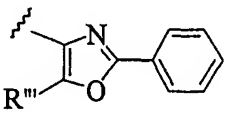
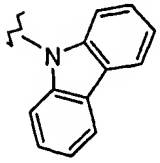
IV

wherein

R' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, or an alkali metal cation;

R is H, C_4-C_{10} aryl, -SO_2(C_1-C_6 alkyl), -SO_2(C_4-C_{10} aryl), -C(O)(C_1-C_6 alkyl), -C(O)(C_4-C_{10} aryl), -CO_2(C_1-C_6 alkyl), -CO_2(C_4-C_{10} aryl),  ,  ,  , or  ;

Y is O, S, or NR;

R" is H, C_4-C_{10} aryl,  ,  ,  , or  ;

R''' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, -SO_2(C_1-C_6 alkyl), -SO_2(C_4-C_{10} aryl), -C(O)(C_1-C_6 alkyl), or -C(O)(C_4-C_{10} aryl);

L, independently for each occurrence, is -CH_2-, O, N, or S;

n is an integer from 0 to 6 inclusive;

m is an integer from 1 to 6 inclusive; and

p is an integer from 0 to 6 inclusive.

91. The compound of claim 90, wherein R' is H.

92. The compound of claim 90, wherein L is -CH_2-.

93. The compound of claim 90, wherein n is 3.

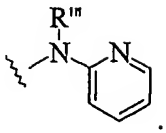
94. The compound of claim 90, wherein m is 2.

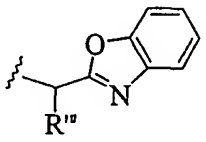
95. The compound of claim 90, wherein p is 1.

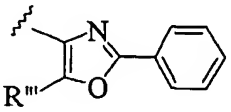
96. The compound of claim 90, wherein R is Ph.

97. The compound of claim 90, wherein Y is O.

98. The compound of claim 90, wherein R" is Ph.

99. The compound of claim 90, wherein R" is  .

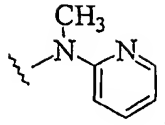
100. The compound of claim 90, wherein R" is  .

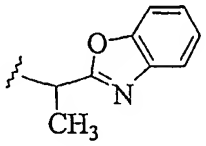
101. The compound of claim 90, wherein R" is  .

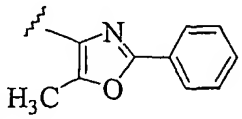
102. The compound of claim 90, wherein R" is 2-naphtyl.

103. The compound of claim 90, wherein R' is H, n is 3, m is 2, p is 1, L is -CH_2-, R is Ph, Y is O, and R" is Ph.

104. The compound of claim 90, wherein R' is H, n is 3, m is 2, p is 1, L is -CH_2-, R is

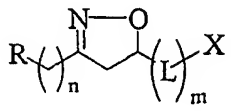
Ph, Y is O, and R" is  .

105. The compound of claim 90, wherein R' is H, n is 3, m is 2, p is 1, L is -CH_2-, R is Ph, Y is O, and R" is  .

106. The compound of claim 90, wherein R' is H, n is 3, m is 2, p is 1, L is -CH_2-, R is Ph, Y is O, and R" is  .

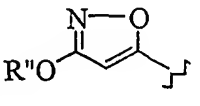
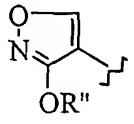
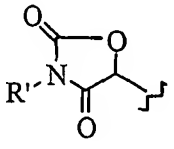
107. The compound of claim 90, wherein R' is H, n is 3, m is 2, p is 1, L is -CH_2-, R is Ph, Y is O, and R" is 2-naphtyl.

108. A compound of formula V:



V

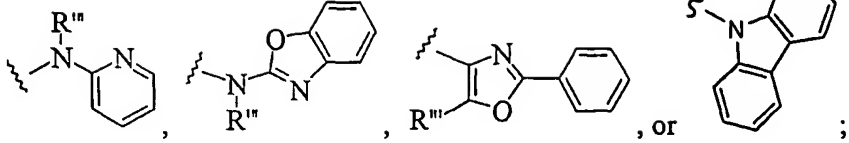
wherein,

R is  ,  , or  ;

R' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, -SO_2(C_1-C_6 alkyl), -SO_2(C_4-C_{10} aryl), -C(O)(C_1-C_6 alkyl), or -C(O)(C_4-C_{10} aryl);

R'' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, or an alkali metal cation;

L, independently for each occurrence, is -CH_2-, O, N, or S;

X is  , or ;

R''' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, -SO_2(C_1-C_6 alkyl), -SO_2(C_4-C_{10} aryl), -C(O)(C_1-C_6 alkyl), or -C(O)(C_4-C_{10} aryl);

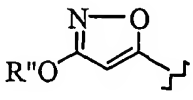
m is an integer from 1 to 6 inclusive; and

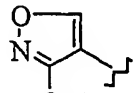
n is an integer from 1 to 6 inclusive.

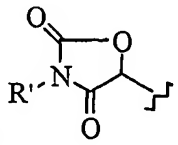
109. The compound of claim 108, wherein R'' is H.

110. The compound of claim 108, wherein R' is -CH_3.

111. The compound of claim 108, wherein n is 1.

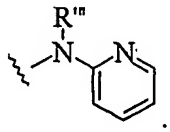
112. The compound of claim 108, wherein R is  .

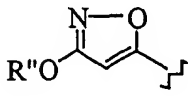
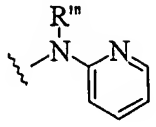
113. The compound of claim 108, wherein R is  .

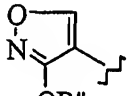
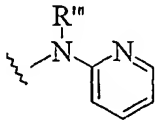
114. The compound of claim 108, wherein R is  .

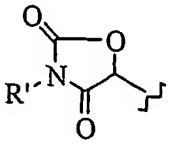
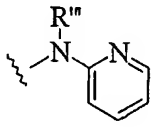
115. The compound of claim 108, wherein L is -CH_2-.

116. The compound of claim 108, wherein m is 3.

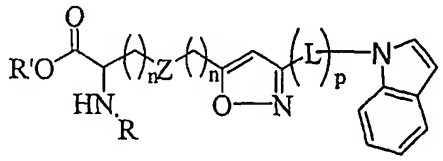
117. The compound of claim 108, wherein X is  .

118. The compound of claim 108, wherein R" is H, n is 1, R' is -CH_3, R is  , L is -CH_2-, m is 3, X is  , and R''' is -CH_3.

119. The compound of claim 108, wherein R" is H, n is 1, R' is -CH_3, R is  , L is -CH_2-, m is 3, X is  , and R''' is -CH_3.

120. The compound of claim 108, wherein R" is H, n is 1, R' is -CH_3, R is  , L is -CH_2-, m is 3, X is  , and R''' is -CH_3.

121. A compound of formula VI:



VI

wherein

R' is H, C_1-C_6 alkyl, C_4-C_{10} aryl, or an alkali metal cation;

R is H, C_1-C_6 alkyl, C_4-C_{10} aryl, -CO(C_1-C_6 alkyl), -CO(C_4-C_{10} aryl), -CO(aralkyl), -CO(aryl(C_2-C_6 alkenyl)), -CO(C_1-C_6 alkyl)C(O)aryl, -CO(C_2-C_6 alkenyl)C(O)aryl, -CO(C_2-C_6 alkenyl)alkyl, -CO_2(C_1-C_6 alkyl)Oaralkyl, -SO_2(C_1-C_6 alkyl), -SO_2(C_4-C_{10} aryl), -CO_2(aralkyl), -CO_2C(C_1-C_6 alkyl)$_3$, aralkyl, or -C(C_1-C_6 alkyl)=CHC(O)aryl;

Z is a bond, O, S, or NR;

L, independently for each occurrence, is -CH_2-, O, N, or S;

n independently for each occurrence, is an integer from 1 to 6 inclusive; and

p is an integer from 1 to 6 inclusive.

122. The compound of claim 121, wherein Z is O.

123. The compound of claim 121, wherein R' is H.

124. The compound of claim 121, wherein n is 1.

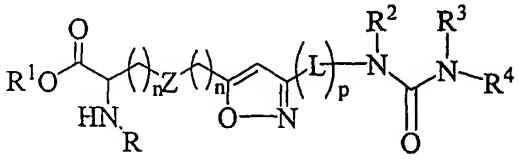
125. The compound of claim 121, wherein L is $-CH_2-$ and p is 4, 5 or 6.

126. The compound of claim 121, wherein R is selected from the group consisting of H, CH_3, $-SO_2CH_3$, $-SO_2Ph$, $-COCH_3$, -COPh, $-CO_2CH_2Ph$, $-CO_2C(CH_3)_3$, $-CH_2Ph$, $-CH_2CH_2Ph$, $-CH_2CH_2CH_2Ph$, and -C(Me)=CHCOPh.

127. The compound of claim 121, wherein R' is H, n is 1, L is $-CH_2-$, and p is 5.

128. The compound of claim 121, wherein Z is O, R' is H, n is 1, L is $-CH_2-$, p is 5, and R is $-CO_2CH_2Ph$.

129. A compound of formula VII:



VII

wherein

R is H, C_1-C_6 alkyl, C_4-C_{10} aryl, $-CO(C_1$-C_6 alkyl), $-CO(C_4$-C_{10} aryl), -CO(aralkyl), $-CO(aryl(C_2$-C_6 alkenyl)), $-CO(C_1$-C_6 alkyl)C(O)aryl, $-CO(C_2$-C_6 alkenyl)C(O)aryl, $-CO(C_2$-C_6 alkenyl)alkyl, $-CO_2(C_1$-C_6 alkyl)Oaralkyl, $-SO_2(C_1$-C_6 alkyl), $-SO_2(C_4$-C_{10} aryl), $-CO_2$(aralkyl), $-CO_2C(C_1$-C_6 alkyl)$_3$, aralkyl, or $-C(C_1$-C_6 alkyl)=CHC(O)aryl;

R^1 is H, C_1-C_6 alkyl, C_4-C_{10} aryl, or an alkali metal cation;

R^2 is H, alkyl, aryl, or aralkyl;

R^3 is H, alkyl, aryl, or aralkyl;

R^4 is aryl or aralkyl;

Z is a bond, O, S, or NR;

L, independently for each occurrence, is $-CH_2-$, O, N, or S;

n independently for each occurrence, is an integer from 1 to 6 inclusive; and

p is an integer from 1 to 6 inclusive.

130. The compound of claim 129, wherein Z is O.

131. The compound of claim 129, wherein R^1 is H.

132. The compound of claim 129, wherein n is 1.

133. The compound of claim 129, wherein L is $-CH_2-$ and p is 3, 4, or 5.

134. The compound of claim 129, wherein R is selected from the group consisting of H, CH_3, $-SO_2CH_3$, $-SO_2Ph$, $-COCH_3$, -COPh, $-CO_2CH_2Ph$, $-CO_2C(CH_3)_3$, $-CH_2Ph$, $-CH_2CH_2Ph$, $-CH_2CH_2CH_2Ph$, and -C(Me)=CHCOPh.

135. The compound of claim 129, wherein R^1 is H, n is 1, L is $-CH_2-$, p is 4, and R is $-CO_2CH_2Ph$.

136. The compound of claim 129, wherein R^2 is alkyl and R^3 is H.

137. The compound of claim 129, wherein R^2 is alkyl and R^3 is H, and R^4 is aryl.

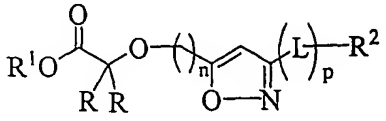
138. The compound of claim 129, wherein R^2 is alkyl and R^3 is H, and R^4 is phenyl or halophenyl.

139. The compound of claim 129, wherein R^1 is H, n is 1, L is $-CH_2-$, p is 4, R is $-CO_2CH_2Ph$, R^2 is alkyl and R^3 is H, and R^4 is aryl.

140. The compound of claim 129, wherein Z is O, R^1 is H, n is 1, L is $-CH_2-$, p is 4, R is $-CO_2CH_2Ph$, R^2 is heptyl, R^3 is H, and R^4 is 2,4-difluorophenyl.

141. The compound of claim 129, wherein Z is O, R^1 is H, n is 1, L is $-CH_2-$, p is 4, R is $-CO_2CH_2Ph$, R^2 is heptyl, R^3 is H, and R^4 is phenyl.

142. A compound of formula VIII:



VIII

wherein

R is H or C_1-C_6 alkyl;

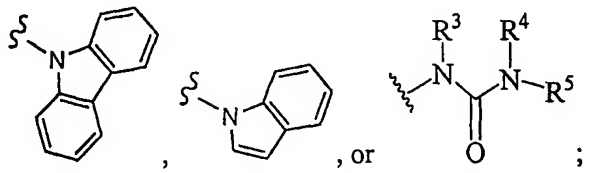
R^1 is H, C_1-C_6 alkyl, C_4-C_{10} aryl, or an alkali metal cation;

L, independently for each occurrence, is $-CH_2-$, O, N, or S;

n independently for each occurrence, is an integer from 1 to 6 inclusive;

p is an integer from 1 to 6 inclusive; and

R^2 is



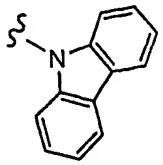
wherein R^3 is H or alkyl; R^4 is H or alkyl; and R^5 is aryl.

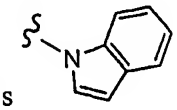
143. The compound of claim 142, wherein R^1 is H.

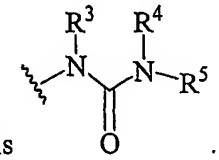
144. The compound of claim 142, wherein n is 1.

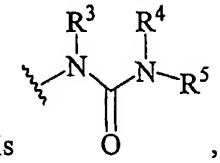
145. The compound of claim 142, wherein L is $-CH_2-$ and p is 3, 4, or 5.

146. The compound of claim 142, wherein R is methyl.

147. The compound of claim 142, wherein R^1 is H, R is methyl, n is 1, L is $-CH_2-$, p is 5, and R^2 is  .

148. The compound of claim 142, wherein R^1 is H, R is methyl, n is 1, L is $-CH_2-$, p is 5, and R^2 is  .

149. The compound of claim 142, wherein R^1 is H, R is methyl, n is 1, L is $-CH_2-$, p is 4, and R^2 is  .

150. The compound of claim 142, wherein R^1 is H, R is methyl, n is 1, L is $-CH_2-$, p is 4, R^2 is  , R^3 is heptyl; R^4 is H; and R^5 is 2,4-difluorophenyl.

151. The compound of any of claims 1-150, wherein said compound is a single stereoisomer.

152. A pharmaceutical composition, comprising a compound of any of claims 1-150; and a pharmaceutically acceptable excipient.

153. A method of modulating a PPAR comprising contacting the PPAR with a compound of claim 1, 19, 70, 90, 108, 121, 129, or 142.

154. A method of treating a mammal afflicted with cancer comprising administering to the mammal a therapeutically effective amount of a compound of claim 1, 19, 70, 90, 108, 121, 129, or 142.

155. A method of treating a mammal afflicted with breast cancer comprising administering to the mammal a therapeutically effective amount of a compound of claim 1, 19, 70, 90, 108, 121, 129, or 142.

156. A method of treating a mammal afflicted with prostate cancer comprising administering to the mammal a therapeutically effective amount of a compound of claim 1, 19, 70, 90, 108, 121, 129, or 142.

157. A method of treating a mammal afflicted with stomach cancer comprising administering to the mammal a therapeutically effective amount of a compound of claim 1, 19, 70, 90, 108, 121, 129, or 142.

158. A method of treating a mammal afflicted with lung cancer comprising administering to the mammal a therapeutically effective amount of a compound of claim 1, 19, 70, 90, 108, 121, 129, or 142.

159. A method of treating a mammal afflicted with colon cancer comprising administering to the mammal a therapeutically effective amount of a compound of claim 1, 19, 70, 90, 108, 121, 129, or 142.

160. A method of treating a mammal afflicted with pancreatic cancer comprising administering to the mammal a therapeutically effective amount of a compound of claim 1, 19, 70, 90, 108, 121, 129, or 142.

161. A method of treating a mammal afflicted with an inflammatory condition or disease, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1, 19, 70, 90, 108, 121, 129, or 142.

162. A method of treating a mammal afflicted with non-insulin-dependent (type II) diabetes, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1, 19, 70, 90, 108, 121, 129, or 142.

163. A method of treating a mammal afflicted with a dyslipidemia, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1, 19, 70, 90, 108, 121, 129, or 142.

Figure 1

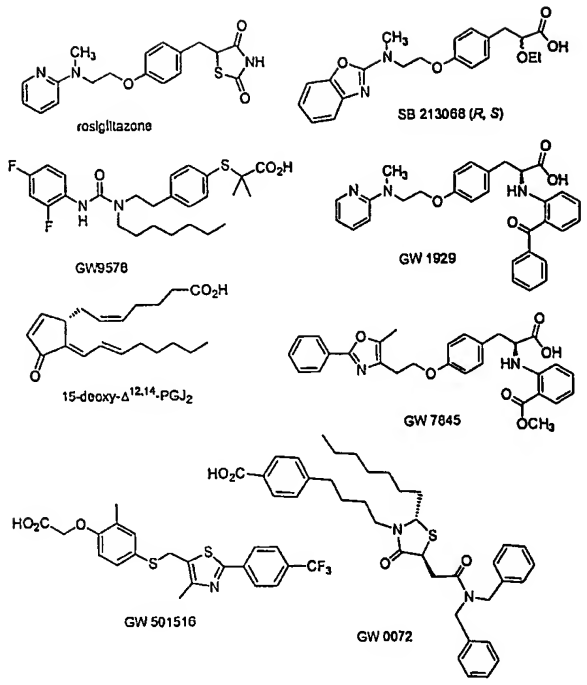

rosiglitazone
SB 213068 (R, S)
GW9578
GW 1929
15-deoxy-Δ12,14-PGJ2
GW 7645
GW 501516
GW 0072

Figure 2

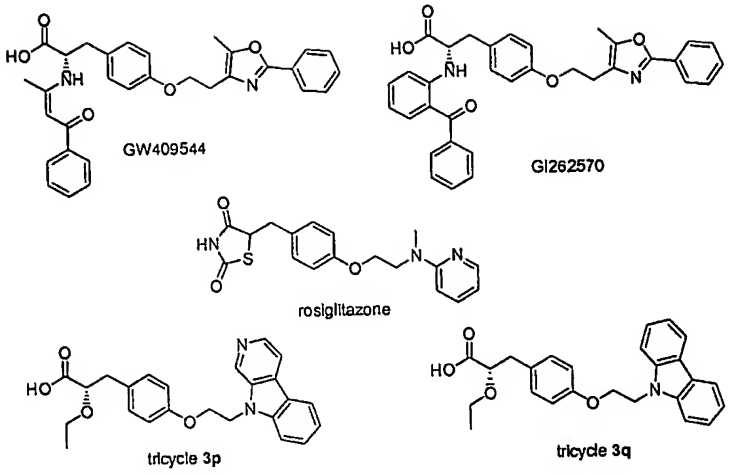


Figure 3

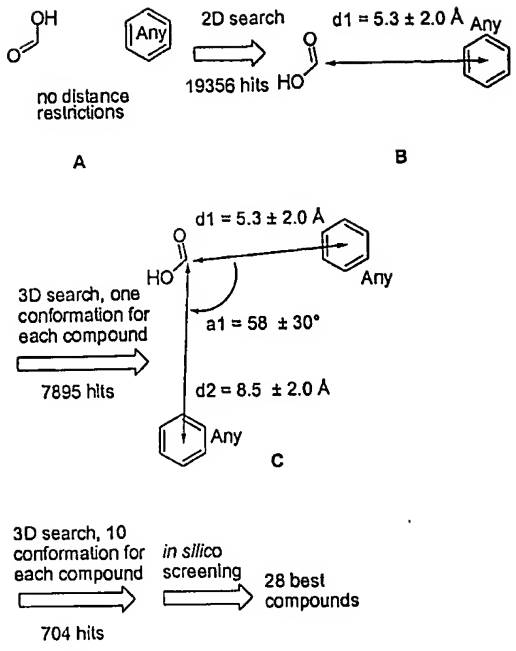

OH
O
Any
2D search
19356 hits
d1 = 5.3 ± 2.0 Å
Any
HO
O
no distance restrictions
A
B
d1 = 5.3 ± 2.0 Å
HO
O
Any
3D search, one conformation for each compound
7895 hits
a1 = 58 ± 30°
d2 = 8.5 ± 2.0 Å
Any
C
3D search, 10 conformation for each compound
704 hits
in silico screening
28 best compounds

Figure 4

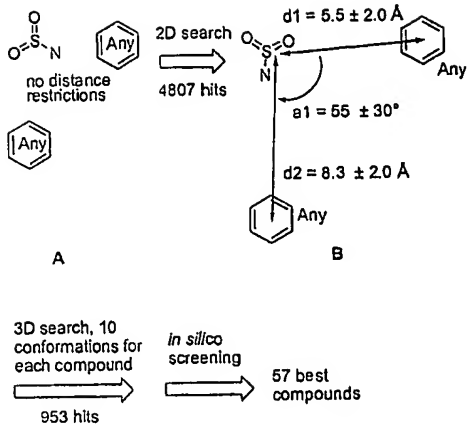

Any
no distance restrictions
2D search
4807 hits
d1 = 5.5 ± 2.0 Å
Any
a1 = 55 ± 30°
d2 = 8.3 ± 2.0 Å
Any
A
B
3D search, 10 conformations for each compound
953 hits
in silico screening
57 best compounds

Figure 5

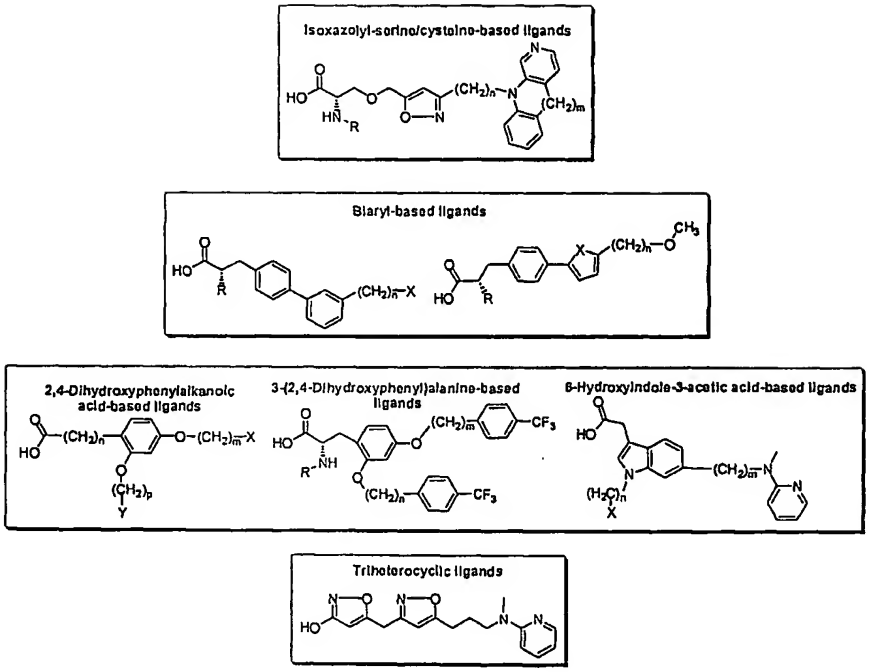

Isoxazolyl-serine/cysteine-based ligands
Biaryl-based ligands
2,4-Dihydroxyphenylalkanoic acid-based ligands
3-(2,4-Dihydroxyphenyl)alanine-based ligands
6-Hydroxyindole-3-acetic acid-based ligands
Triheterocyclic ligands

Figure 6

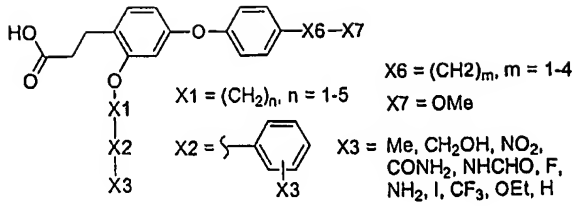

HO
O
O
X1
X2
X3
O
X6–X7
X1 = (CH2)n, n = 1-5
X2 =
X3
X6 = (CH2)m, m = 1-4
X7 = OMe
X3 = Me, CH2OH, NO2, CONH2, NHCHO, F, NH2, I, CF3, OEt, H

Figure 7

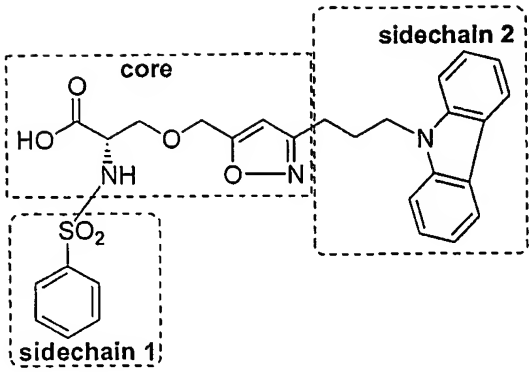


Figure 8

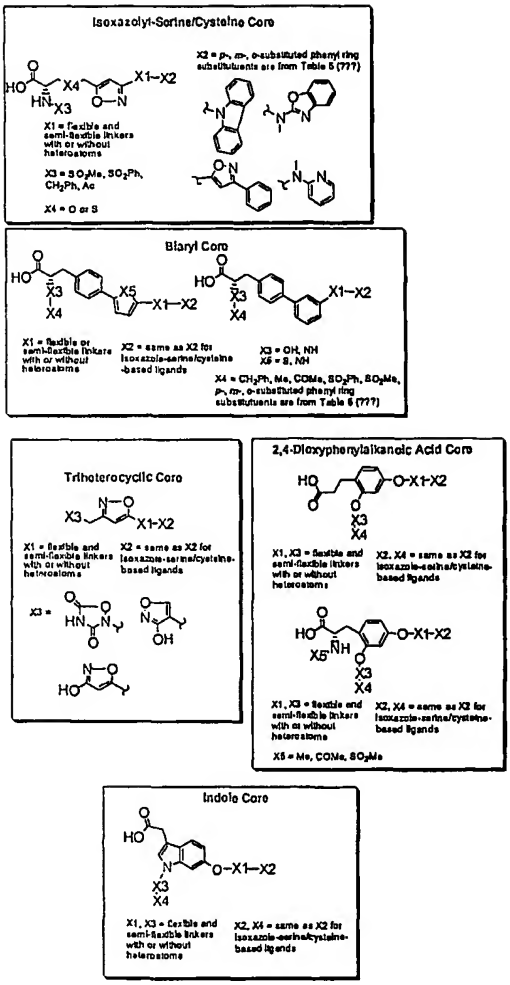

Isoxazolyl-Serine/Cysteine Core
X3 = p-, m-, o-substituted phenyl ring substituents are from Table 5 (???)
X1 = flexible and semi-flexible linkers with or without heteroatoms
X3 = SO2Me, SO2Ph, CH2Ph, Ac
X4 = O or S
Biaryl Core
X1 = flexible or semi-flexible linkers with or without heteroatoms
X2 = same as X2 for isoxazole-serine/cysteine -based ligands
X3 = OH, NH
X5 = S, NH
X4 = CH2Ph, Me, COMe, SO2Ph, SO2Me, p-, m-, o-substituted phenyl ring substituents are from Table 5 (???)
Trihetorocyclic Core
X1 = flexible and semi-flexible linkers with or without heteroatoms
X2 = same as X2 for isoxazole-serine/cysteine-based ligands
X3 =
2,4-Dioxyphenylalkanoic Acid Core
X1, X3 = flexible and semi-flexible linkers with or without heteroatoms
X2, X4 = same as X2 for isoxazole-serine/cysteine-based ligands
X1, X3 = flexible and semi-flexible linkers with or without heteroatoms
X2, X4 = same as X2 for isoxazole-serine/cysteine-based ligands
X5 = Me, COMe, SO2Me
Indole Core
X1, X3 = flexible and semi-flexible linkers with or without heteroatoms
X2, X4 = same as X2 for isoxazole-serine/cysteine-based ligands

Figure 9

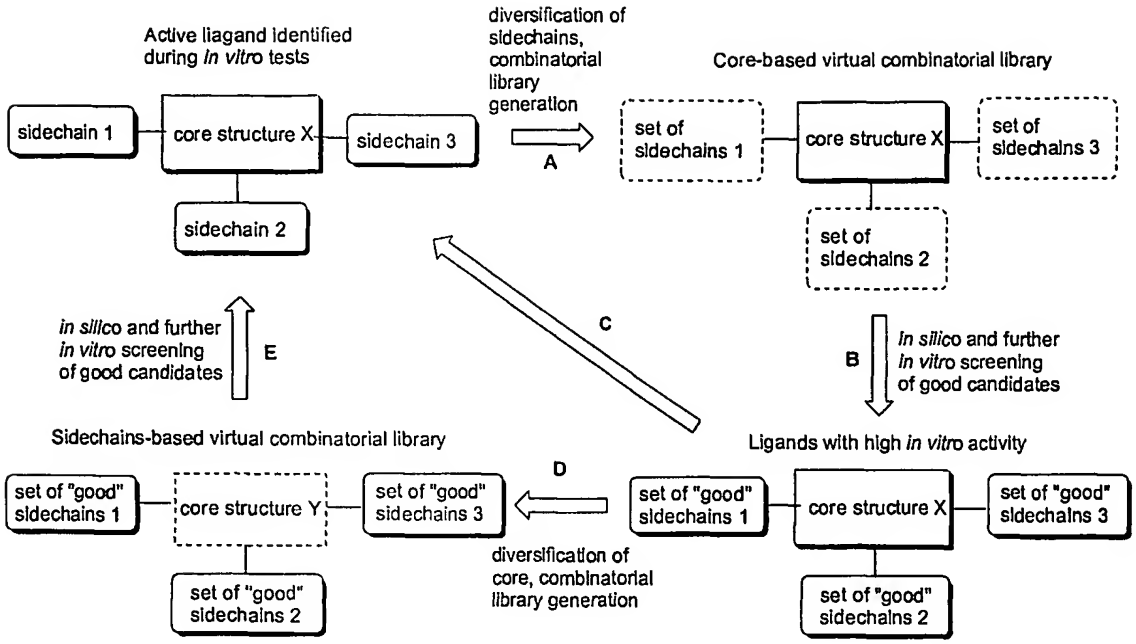

Active liagand identified during *In vitro* tests
diversification of sidechains, combinatorial library generation
Core-based virtual combinatorial library
sidechain 1
core structure X
sidechain 3
sidechain 2
A
set of sidechains 1
core structure X
set of sidechains 3
set of sidechains 2
C
in silico and further *in vitro* screening of good candidates
E
B
In silico and further *in vitro* screening of good candidates
Sidechains-based virtual combinatorial library
Ligands with high *in vitro* activity
D
set of "good" sidechains 1
core structure Y
set of "good" sidechains 3
set of "good" sidechains 2
diversification of core, combinatorial library generation
set of "good" sidechains 1
core structure X
set of "good" sidechains 3
set of "good" sidechains 2

Figure 10

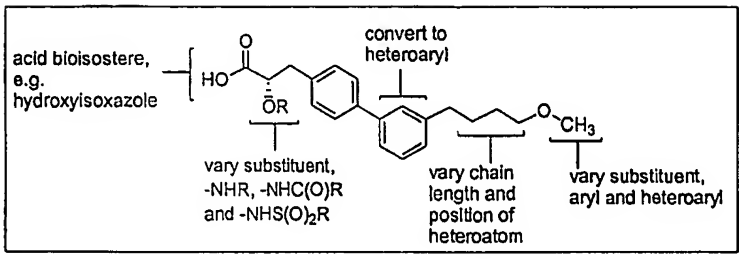

acid bioisostere, e.g. hydroxyisoxazole
HO
O
OR
convert to heteroaryl
O
CH3
vary substituent, -NHR, -NHC(O)R and -NHS(O)2R
vary chain length and position of heteroatom
vary substituent, aryl and heteroaryl

Figure 11

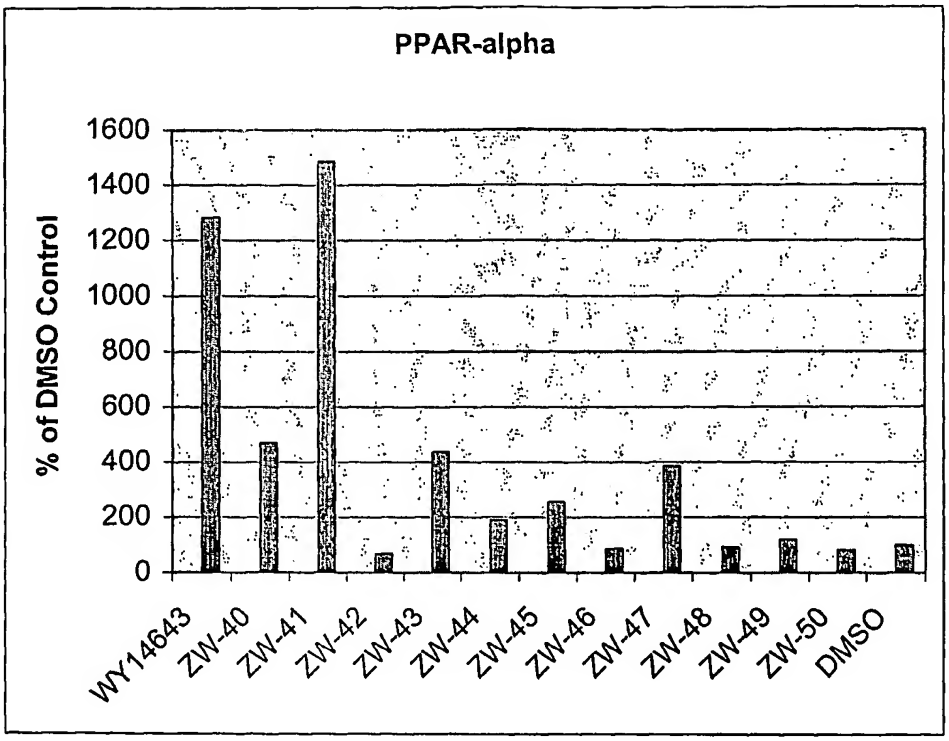

PPAR-alpha
% of DMSO Control
1600
1400
1200
1000
800
600
400
200
0
WY14643
ZW-40
ZW-41
ZW-42
ZW-43
ZW-44
ZW-45
ZW-46
ZW-47
ZW-48
ZW-49
ZW-50
DMSO

Figure 12

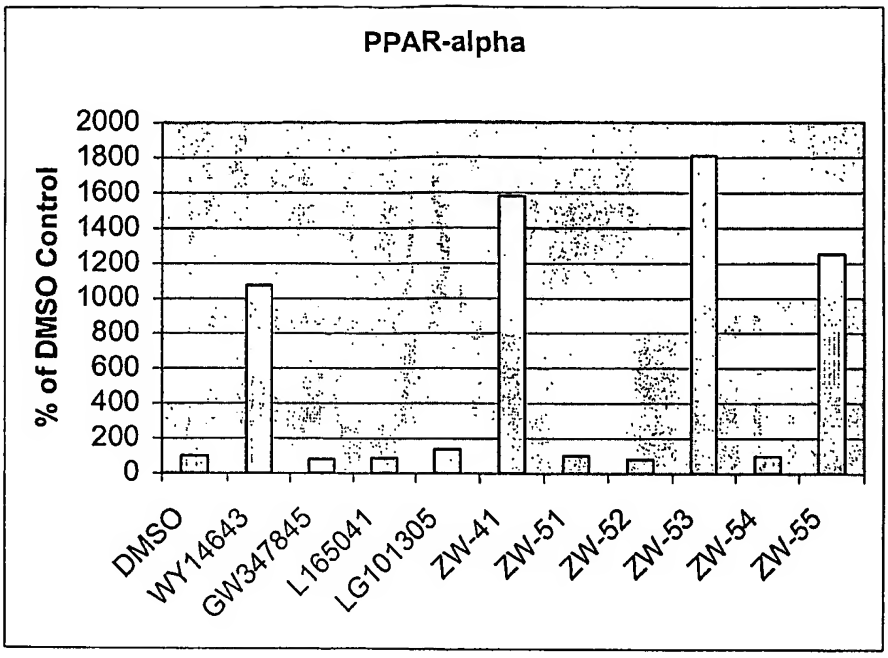

PPAR-alpha
% of DMSO Control
2000
1800
1600
1400
1200
1000
800
600
400
200
0
DMSO
WY14643
GW347845
L165041
LG101305
ZW-41
ZW-51
ZW-52
ZW-53
ZW-54
ZW-55

Figure 13

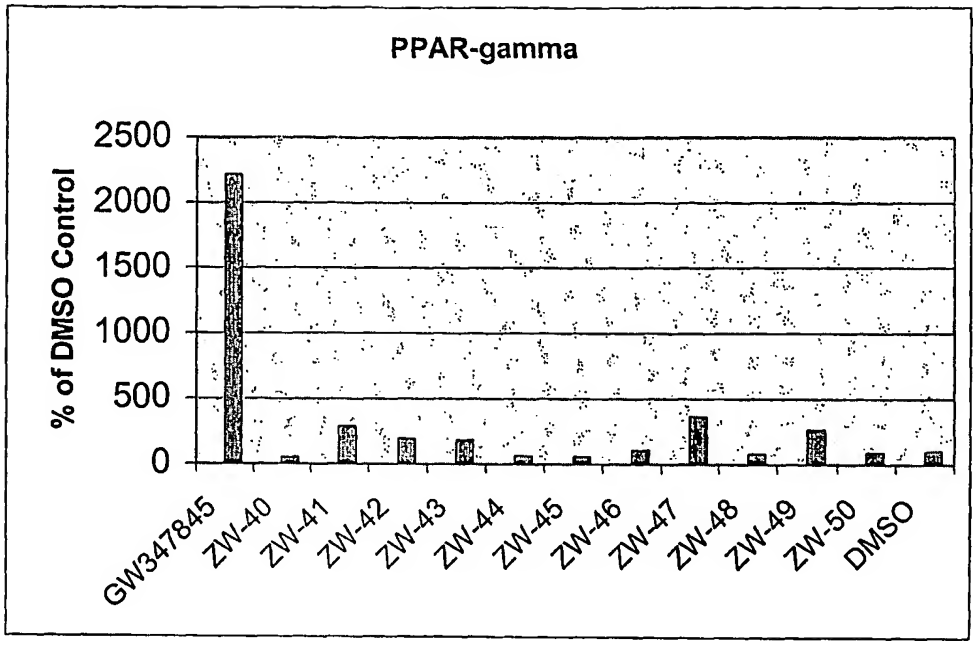

PPAR-gamma
% of DMSO Control
2500
2000
1500
1000
500
0
GW347845
ZW-40
ZW-41
ZW-42
ZW-43
ZW-44
ZW-45
ZW-46
ZW-47
ZW-48
ZW-49
ZW-50
DMSO

Figure 14

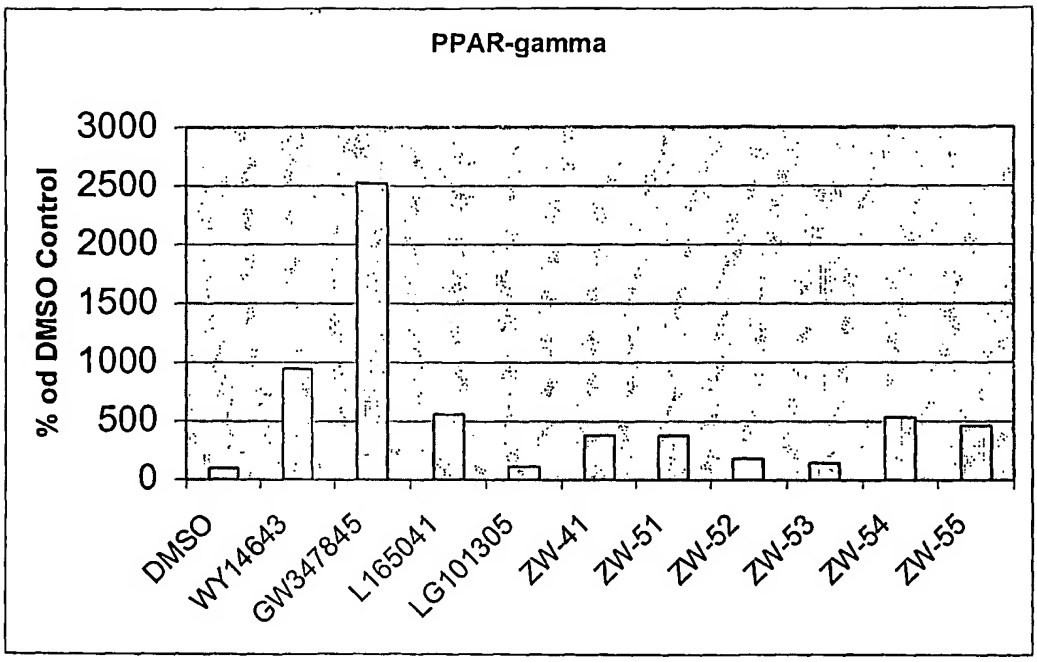

PPAR-gamma
% od DMSO Control
3000
2500
2000
1500
1000
500
0
DMSO
WY14643
GW347845
L165041
LG101305
ZW-41
ZW-51
ZW-52
ZW-53
ZW-54
ZW-55

Figure 15

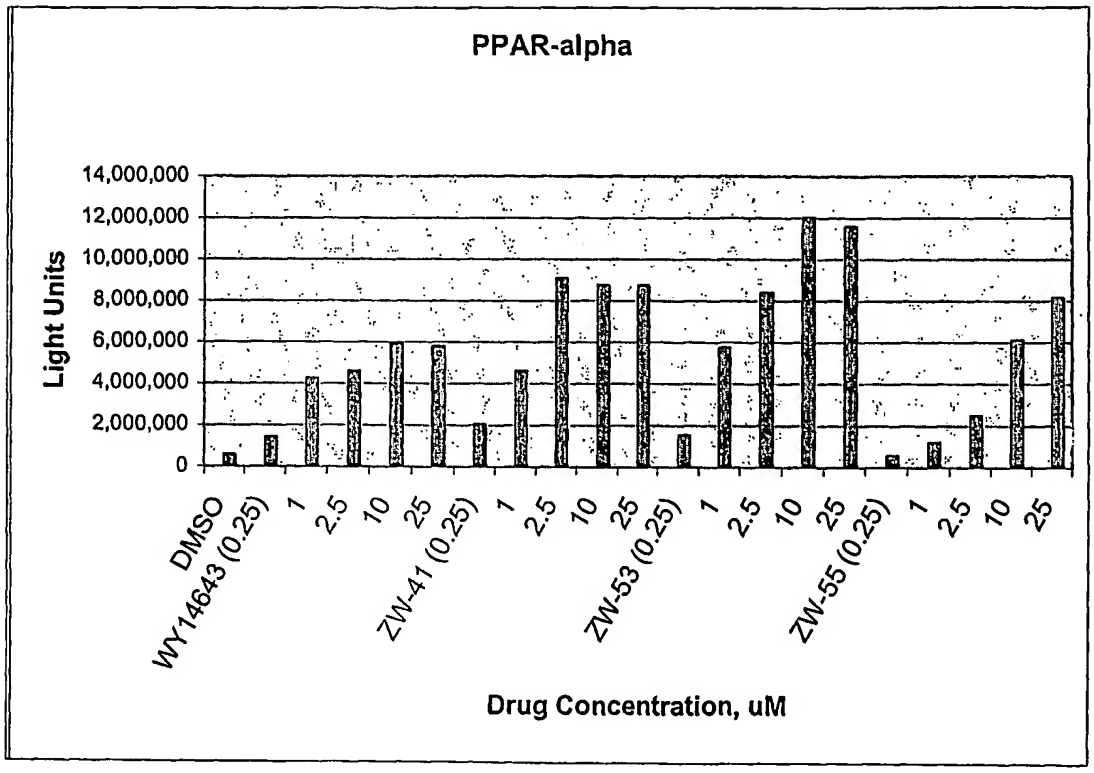
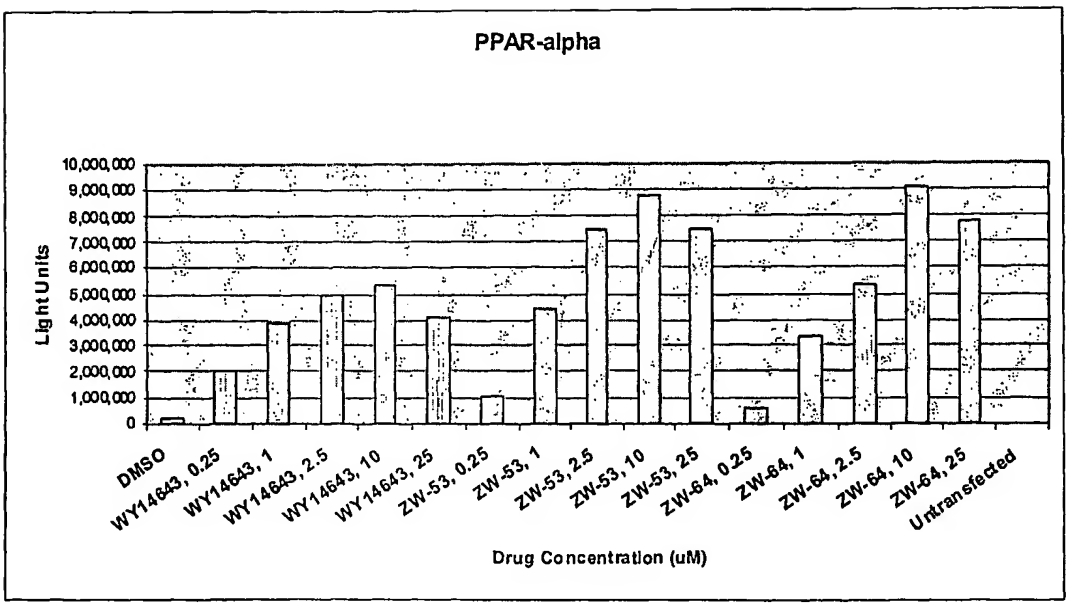

PPAR-alpha
Light Units
14,000,000
12,000,000
10,000,000
8,000,000
6,000,000
4,000,000
2,000,000
0
DMSO
WY14643 (0.25)
1
2.5
10
25
ZW-41 (0.25)
1
2.5
10
25
ZW-53 (0.25)
1
2.5
10
25
ZW-55 (0.25)
1
2.5
10
25
Drug Concentration, uM

Figure 16


PPAR-alpha
Light Units
10,000,000
9,000,000
8,000,000
7,000,000
6,000,000
5,000,000
4,000,000
3,000,000
2,000,000
1,000,000
0
DMSO
WY14643, 0.25
WY14643, 1
WY14643, 2.5
WY14643, 10
WY14643, 25
ZW-53, 0.25
ZW-53, 1
ZW-53, 2.5
ZW-53, 10
ZW-53, 25
ZW-64, 0.25
ZW-64, 1
ZW-64, 2.5
ZW-64, 10
ZW-64, 25
Untransfected
Drug Concentration (uM)